Standardized Low–Molecular-Weight Heparin Bridging Regimen in Outpatients on Oral Anticoagulants Undergoing Invasive Procedure or Surgery
An Inception Cohort Management Study

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Background — Bridging therapy with low–molecular-weight heparin is usually recommended in patients who must stop oral anticoagulants before surgical or invasive procedures. To date, there is no universally accepted bridging regimen tailored to the patient’s thromboembolic risk. This prospective inception cohort management study was designed to assess the efficacy and safety of an individualized bridging protocol applied to outpatients.

Methods and Results — Oral anticoagulants were stopped 5 days before the procedure. Low–molecular-weight heparin was started 3 to 4 days before surgery and continued for 6 days after surgery at 70 anti–factor Xa U/kg twice daily in high-thromboembolic-risk patients and prophylactic once-daily doses in moderate- to low-risk patients. Oral anticoagulation was resumed the day after the procedure with a boost dose of 50% for 2 days and maintenance doses afterward. The patients were followed up for 30 days. Of the 1262 patients included in the study (only 15% had mechanical valves), 295 (23.4%) were high-thromboembolic-risk patients and 967 (76.6%) were moderate- to low-risk patients. In the intention-to-treat analysis, there were 5 thromboembolic events (0.4%; 95% confidence interval, 0.1 to 0.9), all in high-thromboembolic-risk patients. There were 15 major (1.2%; 95% confidence interval, 0.7 to 2.0) and 53 minor (4.2%; 95% confidence interval, 3.2 to 5.5) bleeding episodes. Major bleeding was associated with twice-daily low–molecular-weight heparin administration (high-risk patients) but not with the bleeding risk of the procedure.

Conclusions — This management bridging protocol, tailored to patients’ thromboembolic risk, appears to be feasible, effective, and safe for many patients, but safety in patients with mechanical prosthetic valves has not been conclusively established. (Circulation. 2009;119:2920–2927.)

Key Words: anticoagulants ■ heparin ■ risk factors ■ thrombosis
Generally reduces health costs.\textsuperscript{9,10} In fact, although pharmacy costs are higher with LMWH, total healthcare costs are significantly lower in the LMWH-bridged group through avoidance or minimization of hospital stays and no overall increase of adverse events.\textsuperscript{13} Bridging therapy is more readily accepted in high-thromboembolic-risk patients,\textsuperscript{7,12} whereas methods for managing low- and intermediate-risk patients range from a minimalist strategy involving suspension of oral anticoagulant without administration of heparin\textsuperscript{13} to an aggressive bridging with therapeutic doses of LMWH.\textsuperscript{2,14}

Clinical Perspective on p 2927

Although the validity of perioperative bridging is generally accepted,\textsuperscript{1,15} a single standardized bridging regimen is still lacking, mainly because the published studies are characterized by significant variations in patient population, study design, perioperative anticoagulation regimens, and duration of follow-up.\textsuperscript{1,7,8,12,14} A consensus conference of the Italian Federation of Centers for the Diagnosis of Thrombosis and Management of Antithrombotic Therapies (FCSA) gave rise to a bridging protocol, and recommendations were conveyed to all Italian thrombosis centers, inviting them to participate in a prospective inception cohort study. Here, we report the efficacy and safety of this standardized perioperative bridging protocol with LMWH that is tailored according to the individual thromboembolic risk of patients receiving long-term OAT who required planned temporary interruption of oral anticoagulation before a procedure.

Methods

Study Design

In 2004, the FCSA convened a working group to study the topic of perioperative management of patients on long-term OAT planning to undergo invasive procedures. A consensus conference open to all centers was held in Milan in January 2005. The recommendations on bridging therapy were then published online (http://www.fcsa.it), and all centers were invited to participate in a large-scale multicenter study to investigate the efficacy and safety of the recommended protocol. Twenty-two anticoagulation centers in Italy agreed to participate, and a prospective inception cohort study was conducted between July 2005 and July 2007. The core protocol required each center to collect data about patients on long-term OAT who underwent surgical or invasive procedures and required bridging with LMWH. Patients undergoing simple dental procedures (such as cataract surgery with local anesthesia), in which OAT interruption is not required,\textsuperscript{2} were not included in the study. Data were collected at each center by ad hoc personnel at the time of enrollment and 6 and 30 days after the procedure. Finally, data were reported to the coordination center at the University of Padua Thrombosis Center. This bridging regimen was approved by the local ethics committee at each center and became the standard periprocedural treatment. Informed consent was obtained for each patient.

Anticoagulation Bridging Protocol

To ensure that results were reported consistently, core recommendations defined a set of data tabulations to be produced by all centers. The periprocedural management is outlined in Figure 1. The predefined scheme required interruption of oral anticoagulant 5 days before the planned procedure (ie, 5 doses of the oral anticoagulant were omitted). Bridging with LMWH, according to 2 protocols, was started 1 day after acenocoumarol interruption (day 0) or 2 days after warfarin interruption (day 4). The last dose of LMWH was administered at least 12 hours before the procedure. Bridging with LMWH was resumed at the same preprocedure dosage on day 1 (at least 12 hours after the procedure) or day 2 according to the adequacy of hemostasis, as judged by the surgeon/interventionist, and was continued for at least 6 days or until the INR returned to therapeutic levels. The INR levels were checked on days 5, 0, and 6; additional INR checks were made if necessary at the physician’s discretion. If the INR was above the therapeutic range on day 5 or ≥1.8 on day 1, 1 mg oral vitamin K was given, and the INR was checked the following day. If the INR was below the therapeutic range on day 5, bridging therapy with LMWH was initiated on that same day. If the INR was >1.3 on day 0, procedure postponement was considered.

Oral anticoagulants were resumed on day 1 (if the patient could take oral therapy) at the preoperative maintenance dose plus a boost dose of 50% for 2 consecutive days; maintenance dose was administered from days 3 to 6. After day 6, the oral anticoagulant was continued at an appropriately adjusted dose (based on the preprocedure maintenance dosage) according to the INR levels, and the patient was then managed by the anticoagulation center physician.

Patients with high or low to intermediate thromboembolic risk were stratified according to their indication for OAT.\textsuperscript{17} Criteria for high thromboembolic risk were mechanical mitral valve prostheses, monoleaflet mechanical aortic prostheses or bileaflet aortic prostheses associated with atrial fibrillation or previous arterial embolism, atrial fibrillation associated with previous arterial thromboembolism or mitral valve disease, previous cardiogenic or unexplained systemic embolism, and venous thromboembolism in the previous 3 months.

All other cases were considered low to intermediate thromboembolic risk. Subcutaneous LMWH (nadroparin or enoxaparin) was administered twice daily to high-thromboembolic-risk patients (pro-
tocol A) and once daily, a prophylactic dose, to low- to intermediate-risk patients (protocol B). Doses lower than the therapeutic dose of LMWH were used in protocol A (70 anti–factor Xa U/kg twice daily) because reduced doses minimized complications as previously reported. To improve compliance and avoid errors in dividing the dosage of prefilled syringes, protocol A (Table 1) was designed to satisfy both the original per-kilogram dosage and the commercially available dosages in prefilled syringes. The prophylactic LMWH dosage in protocol B was that recommended in the prevention of venous thromboembolism in orthopedic surgery, weight-adjusted for nadroparin (57 anti–factor Xa U/Kg once daily). Patients (or accompanying family members or caregivers) were instructed by the anticoagulation center nurse how to self-administer LMWH injections at home; in case of difficulty, LMWH administration was performed at home by a nurse.

The choice of the bridging protocol was not affected by the bleeding risk of the procedure. A preplanned analysis of safety outcomes classified procedures as high or low bleeding risk. A high-bleeding-risk procedure was defined as any operation that had an expected duration of >45 minutes and orthopedic, cardiothoracic, vascular, general, urologic, and neurosurgery. All other procedures were classified as low bleeding risk.

### Patients

Outpatients referred to the Italian anticoagulation centers that agreed to participate in the study who required planned temporary withdrawal of OAT before surgical/invasive procedures were considered for this study. Exclusion criteria were age <18 years at the time of recruitment, body weight of <40 kg, renal insufficiency (serum creatinine >2.0 mg/dL), documented contraindication to treatment with LMWH or history of heparin-induced thrombocytopenia, emergency procedures, or procedures not performed as scheduled. Patients undergoing percutaneous coronary intervention with coronary stenting necessitating dual antiplatelet therapy in addition to oral anticoagulants also were excluded. In patients having multiple procedures, data from the first procedure only were considered for analysis.

Each center was requested to report patient demographics, body weight, type of oral anticoagulant, indication for OAT, type and description of surgery/invasive procedure, type of anesthesia used, interval of OAT discontinuation and resumption after the procedure, INR values throughout the perioperative and follow-up periods, type and dosage of LMWH used during the perioperative period, and adverse events with appropriate comments.

### Outcomes and Follow-Up

The primary efficacy outcome was the incidence of thromboembolicism from the OAT interruption (ie, 5 days before the procedure) to 30 days after the procedure. Thromboembolic events were defined as ischemic stroke characterized by sudden neurological deficit in the absence of cerebral hemorrhage at neuroimaging, peripheral or visceral embolism characterized by the occurrence of acute ischemia documented by angiography or surgery in the absence of atherosclerotic occlusive disease, and deep vein thrombosis and pulmonary embolism, objectively documented by compression ultrasonography and computed tomographic scan.

The primary safety outcome was the rate of major bleeding during bridging therapy or during the follow-up period. Major hemorrhage was defined as fatal bleeding causing death, bleeding at critical sites (intracranial, retroperitoneal, intraocular bleeding causing blindness, joint hemorrhage), and clinically overt bleeding either at the site of or at sites different from that of the surgery or procedure and associated with a fall in hemoglobin level of ≥20 g/L in 24 hours and/or requiring unplanned transfusion of ≥2 U of packed red blood cells/whole blood or surgery or angiographic procedure. An expected decrease in hemoglobin level of >20 g/L, planned autotransfusion, and wound bleeding requiring only postponement of bridging therapy were not considered major bleeding. The secondary safety outcome was the incidence of minor bleeding defined as all overt bleeding episodes not satisfying the criteria of major bleeding.

The clinical sequelae were assessed by the healthcare personnel at discharge and 30 days. In this way, late clinical sequelae, which have the highest incidence during the first month after the procedure, would not be overlooked.

### Statistical Analysis

The sample size was determined to achieve a precise estimate of the effectiveness and safety of the protocol. For an estimated mean incidence of major composite adverse events of 3.6% (1.6% thromboembolic and 2.0% hemorrhagic events), as reported by a systematic review and confirmed by recent similar studies, a sample size of 1200 cases was considered appropriate for our study because it would yield a 1.0% margin of error at the 95% confidence level (2-sided significance level = 0.05).

The data were analyzed on the basis of the intention-to-treat principle. Descriptive statistics are reported as appropriate; categorical data are expressed as frequencies (percentage) with their exact binomial 95% confidence intervals (CIs) and compared using the Fisher exact test. Continuous data are reported as mean and SD. Exact logistic regression was used to determine predictors of the primary safety outcome. The data analysis was performed with SAS software, version 9.0 of the SAS System for Windows (SAS Institute Inc, Cary, NC).

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.
Results

Patient and Procedure Characteristics

Overall, 1401 consecutive surgical or invasive procedures were considered in 22 Italian anticoagulation centers during the study period. One hundred thirty-nine were excluded from the study: 46 in patients on dual antiplatelet therapy and OAT, 41 in patients with renal insufficiency, 15 in patients requiring emergency procedures, 2 in patients with a history of heparin-induced thrombocytopenia, and 12 in patients already included for a previous procedure. Moreover, 23 patients were excluded as a result of the procedure not being performed because emergency procedures caused rooms or staff to be unavailable. All other data were analyzed on an intention-to-treat basis. The study was conducted in 1262 patients (Figure 2).

Baseline patient demographics and indications for OAT are shown in Table 2. Patients were predominantly male and treated with warfarin. Two thirds were bridged with nadroparin. Atrial fibrillation was the main indication for OAT, whereas only 15% of the patients had mechanical heart valves (ratio of aortic to mitral valve prosthesis, 3:2).

Overall, 295 patients (23.4%) were bridged with protocol A and 967 (76.6%) with protocol B. The most common reason for intensive bridging treatment (protocol A) was mechanical heart valve prostheses (52.5%), whereas protocol B was used most frequently in atrial fibrillation patients (62.2%). Table 3 illustrates a detailed outline of the surgical and invasive procedures. There were 369 high-bleeding-risk procedures (29.2%); the remaining 893 (70.8%) were classified as low bleeding risk.

Adherence to the Management Protocol

The OAT was stopped between days −5 and −3 in 88% of the patients. Bridging with LMWH began between days −5 and −3 in 90% of the patients. Preprocedure vitamin K was used in 17 episodes, and no one suffered thromboembolic events (3 were prosthetic heart valves). In 1217 of 1262 cases (96.4%), bridging with LMWH was resumed on day 1, and in 268 cases (21.2%), LMWH was continued for >6 days. The resumption of LMWH was on average comparable in low- and high-bleeding-risk procedures (within 24 hours in 99%...
and 98%, respectively). Oral anticoagulant was resumed on day 1 in 71% of the cases and before day 3 in 82% of the cases. The resumption differed between low- and high-bleeding-risk procedures (on day 1 in 82% and 58%, respectively). Baseline mean±SD INRs on day −5 were 2.3±0.5 for atrial fibrillation patients, 2.4±0.6 for venous thromboembolism patients, 2.9±0.6 for mechanical valve patients, 2.4±0.6 for patients with valvular heart disease and biological valve prosthesis, and 2.4±0.6 for patients with other indications. The rate of INR decay was similar in all indications. The applied protocol lowered the INR from a mean±SD of 2.4±0.6 on day −5 to 1.2±0.2 on day 0; the INR values reached a mean±SD of 1.8±0.5 on day 6.

Efficacy and Safety Outcomes

Thromboembolic Events

Five thromboembolic events (0.4%; 95% CI, 0.1 to 0.9), 3 venous and 2 arterial, were recorded during follow-up (Table 4). All events occurred in high-thromboembolic-risk patients, and 1 was fatal. Three events (events 1, 3, and 5 in Table 4) occurred in patients in whom LMWH was not administered according to the assigned protocol. The remaining 2 events occurred in patients not bridged at all: 1 (patient 2) because according to the assigned protocol. The remaining 2 events occurred in patients in whom LMWH was not administered and 1 was fatal. Three events (events 1, 3, and 5 in Table 4) all occurred in high-thromboembolic-risk patients, resulting in an incidence of 5 in 295 (1.7%), a figure that fits well with the range of thromboembolic incidence rate of 0% to 3.6%. We report an incidence of 0.4%, reflecting the general effectiveness of this protocol.

On the whole, there were 53 intermediate or minor bleeding events (4.2%; 95% CI, 3.2 to 5.5). Twenty-seven events were at the procedure site. As with major bleeding, minor bleeding was significantly related to the bridging protocol (protocol A; P<0.0001). Conversely, minor bleeding also was significantly related to the procedure bleeding risk (P=0.0019). Four of the minor bleeding complications required the interruption of LMWH; 30 events required postponing of the OAT; and in the remaining 19 cases, the bridging with LMWH and the OAT were continued unchanged. No heparin-induced thrombocytopenia was reported throughout the follow-up period.

Discussion

This inception cohort prospective management study of LMWH bridging included 1262 procedures in high- and low- to intermediate-thromboembolic-risk patients followed up in Italian anticoagulation centers. Our aim was to assess the efficacy and safety of a standardized management regimen consisting of 2 distinct protocols based on the patient’s thromboembolic risk; we used subtherapeutic doses of nad roparin or enoxaparin in high-thromboembolic-risk patients and prophylactic doses in low- to intermediate-thromboembolic-risk patients. The bleeding risk of the procedure was assessed a posteriori and did not influence the choice of the bridging protocol.

The incidence of thromboembolic events was low. A number of recent studies7,12,14,2022 have reported a thromboembolic incidence rate of 0% to 3.6%. We report an incidence of thromboembolic events at the lower margin of this range (0.4%), reflecting the general effectiveness of this protocol. All 5 thromboembolic events occurred in high-thromboembolic-risk patients (n=295), resulting in an incidence of 5 in 295 (1.7%), a figure that fits well with the reports from recent studies on high-thromboembolic-risk patients requiring bridging therapy. However, all thromboembolic events occurred in patients who were treated with

### Table 4. Thromboembolic Event Details

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Age, y</th>
<th>Indication</th>
<th>Procedure</th>
<th>Event</th>
<th>Event Day*</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F</td>
<td>64</td>
<td>DVT</td>
<td>Hemicolecctomy</td>
<td>PE</td>
<td>5</td>
<td>Thrombosis of the pulmonary artery segmental branches</td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>63</td>
<td>AF+MVR</td>
<td>Saphenectomy</td>
<td>PE</td>
<td>0</td>
<td>No preoperative bridging with LMWH because day −4 INR=3.1</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>83</td>
<td>PE</td>
<td>Femoral osteosynthesis</td>
<td>PE (fatal)</td>
<td>6</td>
<td>History of PE</td>
</tr>
<tr>
<td>4</td>
<td>F</td>
<td>57</td>
<td>AVR+MV repair</td>
<td>Saphenectomy</td>
<td>Systemic embolism</td>
<td>3</td>
<td>No postoperative LMWH because of a considerable surgical site hematoma</td>
</tr>
<tr>
<td>5</td>
<td>F</td>
<td>70</td>
<td>AF+stroke+MVR</td>
<td>Coloscopy</td>
<td>TIA</td>
<td>13</td>
<td>Day 10 INR=2.7</td>
</tr>
</tbody>
</table>

DVT indicates deep vein thrombosis; PE, pulmonary embolism; AF, atrial fibrillation; MVR, mitral valve replacement; AVR, aortic valve replacement; and TIA, transient ischemic attack.

*Number of days after the procedure.
the incorrect bridging regimen or not bridged at all. Therefore, no thromboembolic event would result from an efficacy analysis.

We also found a low incidence of bleeding events (major bleeding, 1.2%). The reported major bleeding incidence varies from 0.9% to 6.7%. Douketis et al applied a minimalist postprocedure protocol by not administering LMWH to patients who underwent high-bleeding-risk procedures and reported a major bleeding incidence of 1.9%. Dunn et al administered therapeutic doses of LMWH after 48 hours to patients at high risk of bleeding and reported a major bleeding incidence of 20.0% for major surgery. We report an incidence of major bleeding of 1.9% in 369 high-bleeding-risk procedures. Furthermore, major surgery was complicated by minor postoperative bleeding in 7.6% of cases. The use of cautious doses of LMWH might be a plausible explanation for these findings. Moreover, it must be emphasized that 7 of 15 major bleeding episodes occurred in patients in whom LMWH was inappropriately resumed the same day of the procedure (within 12 hours). Twice-daily doses of LMWH were related to a higher incidence of both major and minor bleeding but not to the bleeding risk of the procedure. Thus, a priori stratification of patients according to their thromboembolic but not the bleeding risk of the procedure, in addition to the timely resumption of postprocedure LMWH (at the discretion of the treating physician, according to the patient’s hemostatic status), seems reasonable.

Recent studies have considered bridging regimens in either high- or low-thromboembolic-risk patients. Currently, in the literature, there is no generally accepted standardized bridging regimen with LMWH, mainly because studies show significant variations in study design, perioperative anticoagulation regimens, duration of follow-up, and results. Moreover, the regimens studied are based on therapeutic doses of LMWH, and subtherapeutic doses of LMWH are not assessed for efficacy.

We used subtherapeutic doses of enoxaparin or nadroparin on the basis of the results of a registry and consensus of a task force of FCSA investigators. The results of the registry showed that with a mean dose of 64.4 anti–factor Xa U LMWH twice daily, the incidence of bleeding and thromboembolism was in line with that reported in the published literature referring to therapeutic-dose regimens. However, the issue of the use of LMWHs in patients with mechanical heart valves remains unresolved. Although some experts point out that LMWHs provide adequate protection in nonpregnant patients with mechanical heart valve prostheses, recent guidelines raise concern about their use in this setting and recommend the use of unfractionated heparin in the 48 hours preceding the procedure while the INR is <2.7

The adherence to the protocol was overall fairly consistent throughout the study. OAT was stopped as expected 5 days before the procedure, lowering INRs from therapeutic to procedure-safe levels in 98.7% of the cases. Although the use of preoperative vitamin K in the remaining patients was not associated with thromboembolic events, the safety of such an approach cannot be established by our data. LMWH was started on average 4 days before the procedure, not 3 days as the protocol recommended for patients receiving warfarin (94.5%). This may be related to the finding of a subtherapeutic INR on day −5, requiring initiation of LMWH the following day. Because there were no adverse events during the preprocedure period, this aspect of our management regimen seems to need no modification.

We recommended resuming postprocedure LMWH on the first or second postprocedure day, but the final decision was dependent on the operator’s (surgeon/interventionist) judgment of the patient’s hemostatic status. The procedure’s bleeding risk did not affect the LMWH dosage or interval before resumption. In this way, we tried to eliminate errors that might derive from the subjective stratification of the procedure’s bleeding risk. The postprocedure protocol was efficient in bringing the INR levels to 1.8 within 6 days.

Strengths of the present study include its prospective management design, the large size compared with previous studies, and the institution of a standard operator-independent bridging protocol (the surgeon/interventionist could not adjust the LMWH doses but could only postpone its resumption if needed). We tried to limit variability by the following approaches. First, we used a standardized protocol with definite inclusion and exclusion criteria, a priori definition of high- and low-thromboembolic-risk patients, and evaluation of the clinical sequelae by a central committee. Second, the standard follow-up duration of 30 days limited the eventual variability in capturing clinical sequelae and was considered sufficient to ensure that no events were overlooked, considering that thromboembolic events usually occur within several weeks of oral anticoagulation interruption and bleeding events occur within 1 week of the procedure. Third, we performed the analysis on a full intention-to-treat basis. The main limitation of this and other studies is the absence of a control group that would ensure a 2-arm comparison of efficacy and safety in absence and presence of bridging anticoagulation. Other limitations are the relatively small cohort of patients with mechanical prosthetic valves, a follow-up that was too short to identify all potential cases of valve thrombosis and subsequent embolism in this high-risk group, and the lack of a detailed type-specific classification of mechanical valves (not all tilting disk valves have the same thrombogenicity [eg, Medtronic Hall valves]). Hence, the safety of the protocol for these patients has not been conclusively established. Instead, this standardized protocol offers an overall general, not individualized, approach to the problem. In this respect, for a delicate patient such as one with mechanical prosthesis undergoing surgery or procedure, consultation between the anticoagulation physician, cardiologist, and surgeon/interventionist is desirable.

Appendix

The following investigators and anticoagulation centers participated in the study: V. Pengo (Padova); N. Erba (Merate); G. Guazzaloca (Bologna); L. La Rosa (Vimercate); V. De Micheli (Lecco); S. Testa...
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Disclosures

None.

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The management of patients on oral anticoagulant therapy that may require temporary interruption because of planned surgery or procedure is a common yet challenging clinical scenario. In most cases, perioperative bleeding and thromboembolism can be avoided by performing adequate “bridging” with low–molecular-weight heparin. Although the validity of perioperative bridging is generally accepted, a single standardized bridging regimen is still lacking, mainly because the published studies are characterized by significant variations in patient population, study design, bridging regimens, and duration of follow-up. In this large-scale multicenter study, we assessed the safety and efficacy of a generalizable bridging regimen. The use of subtherapeutic doses of low–molecular-weight heparin in high-thromboembolic-risk patients was associated with a very low bleeding incidence on the one hand and a very low thromboembolic incidence on the other. The same effectiveness and safety were observed for prophylactic doses in low- to intermediate-thromboembolic-risk patients. The bleeding risk of the intervention, which because of the lack of general definitions might under many circumstances be a confounder to bridging, was not related to the periprocedural bleeding. This protocol provides anticoagulation centers with a general framework on how to perform bridging in most clinical scenarios. However, as in most circumstances in medicine, each case should be considered individually; in particular, patients with mechanical heart valves might benefit from consultation among the anticoagulation physician, the cardiologist, and the surgeon. The results of this study show that this regimen might be a practical bridging guide in everyday clinical practice.
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