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**THROMBOSIS
WATCH**

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A special thanks to Selma Lopez for editorial oversight



University Health Care
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Review: Peri-Operative Anticoagulation:

A discussion of management of warfarin and antiplatelet agents.

The management of patients on long-term anti-thrombotic therapy who may require temporary disruption for an invasive procedure is challenging. This is an area wherein management is controversial due to methodologically limited prospective data and varied consensus opinion. Yet, this is a commonly encountered clinical problem. Below is a suggested approach to peri-operative anti-thrombotic therapy.

The first issue to consider is anti-platelet agents, particularly aspirin and clopidogrel. Patients are often routinely told to stop all antiplatelet agents 7-10 days before a procedure. While this is probably appropriate for many patients, more attention must be focused in patients with known CAD and stents, particularly drug eluting stents. The major complication of these devices is in stent thrombosis which results in death or MI in over 50% of these patients. Below is a summary of recommendations for managing antiplatelet agents in various clinical settings:^{1,2}

- Drug-eluting stent (DES)**- Delay elective surgery for 1 year if possible, then proceed with surgery with temporary discontinuation of clopidogrel and continuation of aspirin.
- Bare metal stent (BMS)**- Delay elective surgery for at least 6 weeks, then proceed with surgery with temporary discontinuation of clopidogrel and continuation of aspirin.
- If a surgery is performed within the first 12 months after a DES or 6 weeks after a BMS, then continuation of aspirin and plavix is prudent. If the bleeding risk of the surgery precludes the ability to do this, then the patient's cardiologist should be consulted.
- Secondary prophylaxis**- May continue aspirin in very low bleeding risk procedures and discontinue for most others.
- Primary prophylaxis**- Discontinue aspirin 7-10 days before the procedure

For patients on Vitamin K Antagonists such as warfarin, we need to ask 4 questions: ²

1. *Is this a low bleeding risk procedure where there is general consensus that it is safe to continue anti-coagulation (assuming the person performing the procedure concurs)?*

Examples of "low bleeding risk" procedure are:

Arthrocentesis	Dental Extractions	ERCP without sphincterotomy
Vitreoretinal	Derm Excision	EGD +/- biopsy
Cataracts	Moh's Surgery	Colonoscopy +/- Biopsy

2. *Does this patient have a low thromboembolic risk where there is general consensus that bridging therapy is unnecessary?*

Examples of this are:

Single VTE event greater than 12 months-without ongoing risk factors (*cancer, thrombophilia, etc.*)

Bileaflet aortic valve-without additional risk factors (*prior TE, CHF, HTN, DM*)

Atrial Fibrillation – with CHADS score 0-2 and no prior stroke or TIA.

3. *Does the patient have a very high risk of thromboembolism where full-dose bridging is generally recommended?*

Examples of these are:

VTE < 3 months	Valvular atrial fibrillation
Severe Thrombophilia	Atrial fibrillation & CVA or TIA past 3 mos
Mechanical heart valve with TE event <6 months	Mechanical mitral valve
Any older generation heart valve	Atrial fibrillation with CHADS score of 5-6



Review: Peri-Operative Anticoagulation (continued):

4. What are management considerations for patients who do not fit into any of the above three groups?

Examples of these are:

VTE within 3-12 months

Recurrent VTE or active cancer

Mechanical aortic valve with additional risk factors

Atrial fibrillation with CHADS score 3 or 4

Non-severe thrombophilia

For these patients, management decisions must include a careful consideration of the bleeding risk of the proposed surgery along with discussion of patient preferences. It is estimated that the risk of major post-operative bleeding in bridged patients is 0.5-0.7% for minor procedures and 1.8-20% for intermediate-high risk procedures. Also, patient specific risk factors such as: Age>75, Renal Insufficiency, Thrombocytopenia, Anti-platelet agents, liver dysfunction, Epidural/Spinal Anesthesia can increase a patient's bleeding risk: ^{1,3,4,5,6}

For details on risk assessment and protocols for bridging strategies in these patients, please visit our Thrombosis Service website:

http://healthcare.utah.edu/thrombosis/professionals/protocols/bridging_worksheet.pdf

¹ Grines, C.L., et al., Prevention of premature discontinuation of dual antiplatelet therapy in patients with coronary artery stents: a science advisory from the American Heart Association, American College of Cardiology, Society for Cardiovascular Angiography and Interventions, American College of Surgeons, American Dental Association, with representation from the American College of Physicians. *Circulation*, 2007.

² Douketis JD, Berger PD, Dunn AS, et.al. The Perioperative Management of Antithrombotic Therapy: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition) *Chest* 2008; 133;299-339

³ Kovacs MJ. et al. Single-arm study of bridging therapy with low-molecular-weight heparin for patients at risk of arterial embolism who require temporary interruption of warfarin. *Circulation*. 2004 Sep 21;110 (12):1658-63

⁴ Douketis JD, Johnson JA, Turpie AG. Low-molecular-weight heparin as bridging anticoagulation during interruption of warfarin: assessment of a standardized periprocedural anticoagulation regimen. *Archives of internal medicine*. 2004 Jun 28;164(12):1319-26

⁵ Kearon C, Hirsh J. Management of anticoagulation before and after elective surgery. *The New England Journal of medicine*. 1997 May 22;336(21):1506-11

⁶ Dunn AS, Spyropoulos AC, Turpie AG. Bridging therapy in patients on long-term oral anticoagulants who require surgery: the Prospective Peri-operative Enoxaparin Cohort (PROSPECT). *J Thromb Haemost*. 2007 Nov;5(11):2211-8



WHAT'S NEW IN THE LITERATURE?

JOURNALS REVIEWED: AMERICAN JOURNAL OF HEMATOLOGY, AMERICAN JOURNAL OF MEDICINE, ARCHIVES OF INTERNAL MEDICINE, Chest, Journal of the American College of Cardiology, Journal of the American Medical Association, Journal of Thrombosis and Haemostasis, Lancet, Thrombosis and Haemostasis

1. A new standard for thromboprophylaxis after orthopedic surgery?

Rivaroxaban versus enoxaparin for thromboprophylaxis after hip arthroplasty. Eriksson BI, Borris LC, Friedman RJ, et. al. N Engl J Med 2008;358:2765-75.

Rivaroxaban versus enoxaparin for thromboprophylaxis after total knee arthroplasty. Lassen MR, Ageno W, Borris LC, et. al. N Engl J Med 2008;358:2776-86.

These very similar, randomized, double-blind trials conducted by the RECORD1 and RECORD3 study groups compared an oral direct factor Xa inhibitor with enoxaparin for thromboprophylaxis after orthopedic surgery. The primary efficacy outcome in both studies was the composite of any DVT, nonfatal PE, or death from any cause. Secondary efficacy outcomes included major VTE (proximal DVT, nonfatal PE, or death from VTE). Both studies used a once-daily, 10 mg oral dose of rivaroxaban and a once-daily 40 mg subcutaneous dose of enoxaparin.

The RECORD1 study randomized 4541 patients undergoing total hip arthroplasty to receive 35 days of thromboprophylaxis. This was followed by bilateral venography, and then an additional follow-up visit occurred about a month after the last dose of the study drug. VTE or death occurred in 1.1% in the rivaroxaban group and in 3.7% in the enoxaparin group (absolute risk reduction, 2.6%; 95% CI, 1.5 to 3.7; $P<0.001$). Major VTE occurred in 0.2% in the rivaroxaban group and in 2.0% in the enoxaparin group (absolute risk reduction 1.7%; 95% CI, 1.0 to 2.5; $P<0.001$). Major bleeding occurred in 0.3% in the rivaroxaban group and 0.1% in the enoxaparin group ($P=0.18$).

The RECORD3 study randomized 2531 patients undergoing total knee arthroplasty to receive 10 to 14 days of thromboprophylaxis. Bilateral venography was performed at the end of this time, and patients were followed for 30 to 35 days after the last dose of study medication. VTE or death occurred in 9.6% who received rivaroxaban and in 18.9% who received enoxaparin (absolute risk reduction, 9.2%; 95% CI, 5.9 to 12.4; $P<0.001$). Major VTE occurred in 1.0% given rivaroxaban and 2.6% given enoxaparin (absolute risk reduction, 1.6%; 95% CI, 0.4 to 2.8; $P=0.01$), and symptomatic VTE also occurred less frequently ($P=0.005$). Major bleeding occurred in 0.6% of patients in the rivaroxaban group and 0.5% in the enoxaparin group.

Together these phase 3 trials suggest that rivaroxaban is more effective than once daily enoxaparin in preventing VTE after orthopedic surgery with similar rates of bleeding. These studies unfortunately did not use the dosing of enoxaparin (30 mg SQ bid) which is recommended in the United States for these orthopedic surgeries.



WHAT'S NEW IN THE LITERATURE (CONTINUED)?

2. Selecting pulmonary embolism patients for early discharge – cautionary note.

Length of hospital stay and postdischarge mortality in patients with pulmonary embolism. Aujesky D, Stone RA, Kim S, et. al. Arch Intern Med 2008;168:706-712.

This retrospective analysis examined 15,531 patient discharges with PE in the state of Pennsylvania. The goal was to identify patient and hospital factors associated with length of stay (LOS) and assess whether LOS was associated with postdischarge mortality. The authors quantified severity of illness using the Pulmonary Embolism Severity Index (PESI). LOS was defined by quartiles (≤ 4 days, 5-6 days, 7-8 days, and >8 days). The median LOS was 6 days, the overall mortality rate was 9.3%, and the postdischarge mortality rate was 3.3%. Factors associated with greater LOS included greater severity of illness, lack of private health insurance, black race, and the patient being from Philadelphia. Adjusted postdischarge mortality was significantly higher for patients with an LOS of 4 days or less (OR, 1.55; 95% CI, 1.21-2.00) relative to those with an LOS of 5 to 6 days. This increased mortality suggests that physicians may have inappropriately selected patients for early discharge. As evidence of this, more than half of the patients hospitalized for 4 days or less were higher-risk patients (PESI risk classes III-V), and patients with the highest PESI risk class were almost as likely to be discharged within 4 days as the lowest-risk patients (19% vs. 26%). Given the mortality associated with PE, careful selection of patients for early discharge is clearly needed

3. Clopidogrel does'nt benefit patients undergoing arteriovenous fistula creation.

Effect of clopidogrel on early failure of arteriovenous fistulas for hemodialysis. Dember LM, Beck GJ, Allon M, et. al. JAMA 2008;299:2164-2171.

In this randomized, double-blind, placebo-controlled trial, 877 patients with end-stage renal disease or advanced chronic kidney disease received clopidogrel (300 mg loading dose followed by daily dose of 75 mg) or placebo for 6 weeks starting within 1 day of fistula creation. Data collection was performed at baseline, 6 weeks after fistula creation, and monthly thereafter until ascertainment of fistula suitability. The primary outcome was thrombosis 6 weeks after fistula creation, and the major secondary outcome was failure to attain suitability for dialysis. Fistula thrombosis occurred in 12.2% of patients assigned to clopidogrel compared with 19.5% of patients assigned to placebo (relative risk, 0.63; 95% CI, 0.46-0.97; $P=0.018$). Failure to attain suitability for dialysis did not differ between the clopidogrel and placebo groups (61.8% vs. 59.5%, respectively; relative risk 1.05; 95% CI, 0.94-1.17; $P=0.40$). This unusually large vascular access trial suggests that clopidogrel prevents fistula thrombosis but does not impact the clinically relevant endpoint of fistula suitability. By preventing thrombosis of fistulas that are doomed to fail, clopidogrel may actually delay the achievement of suitable long term dialysis access.



WHAT'S NEW IN THE LITERATURE (CONTINUED)?

4. Does dietary protein affect warfarin dose response?

Potential interaction between warfarin and high dietary protein intake. Hornsby LB, Hester EK, Donaldson AR. *Pharmacotherapy* 2008; 28:536-9.

A 55-year-old male was receiving anticoagulation with warfarin 95 mg/week for aortic valve replacement. His INR was stable on this dose for 5 weeks when his INR began to steadily decrease in the presence of no other remarkable causes. Finally it was discovered that at the time of initial INR decrease, the patient began a low-carbohydrate, high-protein diet and was maintaining a state of ketosis through urine ketone testing. The patient was stabilized on 110 mg/week of warfarin, a 16% increase from his previous therapeutic dose. When the patient discontinued the low-carbohydrate, high-protein diet his INR correspondingly increased. His INR stabilized on his previous warfarin dose of 95 mg/week. Possible mechanisms of a warfarin-dietary protein interaction presented by the authors include increased warfarin protein-binding (less free warfarin available for effect) and induction of the CYP enzyme system that metabolizes warfarin. Of these two, the authors believe the increased metabolism of warfarin is the more plausible explanation, given that increased protein binding would likely be a transient effect.

5. The Role of PCC in rapid warfarin reversal?

Prothrombin complex concentrate (Beriplex® P/N) for emergency anticoagulation reversal: a prospective multinational clinical trial. Pabinger I, et al. *J Thromb Haemost* 2008; 6:622-31.

This single-arm prospective multi-center study was designed to evaluate the safety and efficacy of Beriplex® P/N prothrombin complex concentrate (PCC) dosing stratified based on baseline INR. Patients were enrolled if they were taking oral anticoagulation therapy, had an INR > 2, and required either emergency surgical or urgent invasive diagnostic intervention or required INR normalization as a result of acute bleeding. Patients received Vitamin K as determined by each study center (either oral, IV, or SC), and then the following doses of PCC based on baseline INR:

Baseline INR	PCC Dose
2.0-3.9	25 IU/kg
4.0-6.0	35 IU/kg
> 6	50 IU/kg

The primary study endpoint was the normalization of the INR (defined as ≤ 1.3) 30 minutes following the end of the PCC infusion. A total of 43 patients were enrolled in the study; 40% were taking phenprocoumon, 40% acenocoumarol, and 20% warfarin. Twenty-six patients were undergoing interventional procedures, and 17 patients were experiencing acute bleeding. Vitamin K was given in 38 patients (88%), at varying routes and dosages. The INR normalized to ≤ 1.3 in 40 patients (93%) 30 minutes post-PCC infusion. The INR was 1.4 in the remaining three patients. Throughout the 48-hour observation period the INR remained stable between 1.2 and 1.3. Clinical hemostatic efficacy as judged by physician rating was "very good" in 40 patients (93%), "satisfactory" in two patients, and "questionable" in one patient. There was one adverse event (a fatal pulmonary embolism) that was determined to be "possibly" related to PCC infusion. The conclusion from this study is that Beriplex® P/N is effective in reducing the INR promptly and at the same time achieving clinical hemostatic efficacy.



WHAT'S NEW IN THE LITERATURE (CONTINUED)?

6. What are the risks of combining warfarin and an antiplatelet agent?

Outcomes associated with combined antiplatelet and anticoagulant therapy. Johnson SG, Rogers K, Delate T, Witt DM. Chest 2008; 133:948-54.

This is a retrospective, longitudinal cohort analysis that is a follow-up to a previous study finding high prevalence of dual oral anticoagulant/antiplatelet therapy. The goal was to document the rate of anticoagulation-related adverse events and coronary events in patients receiving combined therapy versus those receiving warfarin monotherapy. The study was conducted through the Kaiser Permanente Colorado Pharmacy Anticoagulation Service. The study included 4,183 patients (2,560 warfarin monotherapy and 1,623 combination-therapy). The prevalence of combined therapy was 388 per 1,000 patients, with aspirin 81 mg daily being the most common antiplatelet agent used. INR control was worse in the combination therapy group (lower % INRs in range, higher % INRs ≤ 1.5 or ≥ 4.5). Patients in the combination therapy group had a statistically significantly higher rate of anticoagulation-related hemorrhagic events than the monotherapy group (4.2% vs 2.0%, unadjusted $p < 0.001$), mostly in the form of epistaxis and GI bleeding. When adjusted for confounding factors, the odds ratio (OR) for an anticoagulation-related hemorrhagic event was 2.75 (95% CI, 1.44-5.28) for the combination therapy group. There was no difference between groups in anticoagulation-related thrombosis or death, and no difference in coronary events after adjustment for confounders (adjusted OR 0.99; 95% CI 0.37-2.62). These results further emphasize the importance of weighing the risk:benefits before adding an antiplatelet agent to anticoagulant therapy.

7. How common are thrombotic events in the setting of severe sepsis?

Levine R.L., LeClerc J.R., Bailey J.E., Monberg M.J., and Sarwat S. Venous and Arterial Thromboembolism in Severe Sepsis. Thromb Haemost. 2008; 99: 892-898.

The burden of thromboembolism (TE) in severe sepsis is largely unknown. This study evaluated composite data from three clinical trials [evaluating the use of drotrecogin alfa (activated) (DrotAA) and an inhibitor of secretory phospholipase A₂ (sPLA₂)] to determine the cumulative 28-day incidence of TE in patients with severe sepsis. The 2,649 patients included in the analysis had a mean age of 59.9 years and a mean initial APACHE II score of 24.6. Fifty-percent of subjects were receiving heparin thromboprophylaxis. During 28 days of follow up, 3.2% of patients developed a TE event; 1.1% ischemic stroke, 1% VTE, 0.9% acute coronary syndrome, and 0.2% other. Arterial events had a higher peak in the first five days, whereas VTE incidence occurred at a constant rate throughout the 28 days. Subgroup analysis noted TE rates of 2.0% in patients treated with DrotAA, 3.5% placebo, and 4.0% sPLA₂. The conclusions of this study are that TE events are common in patients with severe sepsis and that arterial events may be more common than previously appreciated. Understanding the burden of events will be helpful in designing future interventions.

8. Mining the genome to predict recurrent VTE- does it work?

Van Hylckama Vlieg A, Baglin CA, Bare LA, Rosendaal FR, Baglin TP. Proof of principle of potential clinical utility of multiple SNP analysis for prediction of recurrent venous thrombosis. J Thromb Haemost 2008;6: 751-4.

Recurrent venous thromboembolism (VTE) is problematic, particularly in patients with unprovoked VTE in whom the annual recurrence risk is approximately 5% after completing 3-6 months of anticoagulant therapy. Although associated with a first episode of VTE, single thrombophilic disorders (e.g. Factor V Leiden and Prothrombin 20210A mutation) do not predict recurrence risk. This study evaluated the utility of multiple single nucleotide polymorphism (SNP) analysis to predict future recurrent VTE in 817 unselected patients with a first episode of VTE followed for a mean duration of 4.6 years. The overall incidence rate of recurrence was 30.8/1000 person years, corresponding with a 3.1% annual risk. No single SNP was more than weakly associated with recurrence risk. Although multiple SNPs were increasingly predictive of recurrence (2.7-fold and 5.1-fold increase risk for carriers of three and four SNPs respectively), only 2.3% of the cohort carried three or more SNPs. Although corresponding to increased risk of recurrent VTE, the infrequency of multiple SNP carriers limits the clinical usefulness of this approach.



WHAT'S NEW IN THE LITERATURE (CONTINUED)?

9. Do cancer outpatients benefit from primary thromboprophylaxis?

Khorana A.A., Kuderer N. M., Culakova E., Lyman G.H., and Francis C.W. Development and Validation of a Predictive Model for Chemotherapy-Associated Thrombosis. *Blood*. 2008; 111: 4902-4907.

Cancer is associated with a 4.1-fold increased risk of VTE and chemotherapy with a 6.5-fold increased risk. Further, VTE is a leading cause of death in cancer patients. Yet, primary thromboprophylaxis in cancer outpatients receiving chemotherapy has not consistently been shown to be beneficial. This current study evaluated data from 4066 cancer patients enrolled in the ANC study group registry (patients receiving newly initiated chemotherapy) to develop a VTE risk prediction model. Derivation and validation cohorts consisted of 2701 and 1365 patients respectively who were followed for a median of 73 days.

Patient characteristic	Risk score
Site of cancer	
Very high risk (stomach, pancreas)	2
High risk (lung, lymphoma, gynecologic, bladder, testicular)	1
Prechemotherapy platelet count $350 \times 10^9/L$ or more	1
Hemoglobin level less than 100 g/L or use of red cell growth factors	1
Prechemotherapy leukocyte count more than $11 \times 10^9/L$	1
BMI 35 kg/m^2 or more	1

Applying this risk score, those with 3 or greater points had a 7.1% and 6.7% risk of VTE in the derivation and validation cohorts respectively over approximately 2 months of follow-up. The results of this study are important in setting the stage for future clinical trials to determine if implementing primary thromboprophylaxis in these high risk patients can improve outcomes. In the interim, management is left to clinical judgment, but for the majority of patients, the 2008 ACCP guidelines recommend against primary prophylaxis in cancer outpatients receiving chemotherapy (*Chest* 2008; 133: 381S-453).



NEW PRACTICE GUIDELINE ALERT:

THE 2008 AMERICAN COLLEGE OF CHEST PHYSICIANS (ACCP) GUIDELINES ARE HERE!

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WWW.CHESTJOURNAL.ORG

UNIVERSITY HEALTHCARE THROMBOSIS SERVICE NEWS AND EVENTS

General:

- Welcome to Steve Robison who has joined our inpatient clinical-research nurse team!!
- The University of Utah Health Care warfarin education booklets are now available in Spanish.
- The University of Utah Thrombosis Service, in conjunction with the Departments of Pharmacy Services and Quality and Patient Safety is actively involved in assuring compliance with the 2008 JCAHO Safety Guidelines related to anticoagulation.

Research:

- Congratulations to Sara Vazquez for her publication on the effects of azathioprine on warfarin dosing requirements!
- Bob Pendleton and Pam Proctor were awarded a UUMG-QI grant to look at improving the transition of care in patients newly started on warfarin who are discharged from the hospital.
- The Thrombosis Service research group is actively recruiting patients for numerous clinical trials, including:
 1. ADOPT: Oral Apixaban for DVT prevention in the medically-ill
 2. RE-SONATE: Oral Dabigatran for secondary VTE prevention
 3. EMPEROR: A multi-center ED-based pulmonary embolism registry
 4. VTE in the Elderly
 5. Evaluating FDG-PET CT scan in patients with acute venous thromboembolism

Education:

We are in the process of revising our journal club format and working to ensure that CE credit is offered.

**NEXT JOURNAL CLUB IS SEPT 4th at 6:00 PM. Location: HSEB 2938.
We will be reviewing the ACCP guidelines on VTE treatment and prevention**



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Thrombosis Service

QUESTIONS

1. In patients with a cardiac stent who are receiving dual anti-platelet therapy and require a surgical procedure, which of the following is a true statement with regards to guideline recommended management?
 - a. Interruption of dual anti-platelet therapy should be avoided for at least one year after drug-eluting stent (DES)
 - b. Interruption of dual anti-platelet therapy should be avoided for at least 6 weeks after bare metal stent
 - c. If surgery is performed in patients with a DES after 12 months, aspirin should be continued through peri-operative period if possible.
 - d. All the above
2. In a large Pennsylvania cohort study of patients with acute pulmonary embolism, what was the risk (OR =odds ratio) of post-discharge mortality in patients who had the lowest quartile of length-of-stay (<4 days)?
 - a. OR = 1.55
 - b. OR = 1.0
 - c. OR = 0.75
 - d. OR = 0.5
3. Which of the following is considered a low-bleeding risk procedure wherein no interruption of chronic warfarin therapy is required?
 - a. Arthrocentesis
 - b. Cataract surgery
 - c. Dermatologic excisions
 - d. All the above
4. Which of the following conditions are associated with a relatively low risk of thromboembolic complications and so NO “bridging” therapy is required during short term periods of warfarin interruption?
 - a. Atrial fibrillation with a CHADS₂ score of 4-5.
 - b. Mechanical mitral valve without additional risk factors
 - c. DVT/PE 12 months ago with no ongoing risk factors
 - d. Mechanical aortic valve in the setting of heart failure
5. Which of the following agents was shown to be superior to 40mg once-daily enoxaparin for the prevention of venous thromboembolism in patients undergoing joint replacement surgery?
 - a. Rivaroxaban, an oral Xa-inhibitor, 20mg twice-daily
 - b. Rixaroxaban, a direct thrombin inhibitor, 10mg once daily
 - c. Rivaroxaban, an oral Xa-inhibitor, 10mg once daily
 - d. None of the above. The treatments were equivalent.
6. Which of the following are independently associated with an increased risk of DVT/PE in outpatients with cancer undergoing chemotherapy?
 - a. “Very high risk” cancer such as pancreatic or stomach
 - b. BMI of 35 kg/m² or greater
 - c. Pre-chemotherapy platelet count of 350 x 10⁹/L or more
 - d. All the above

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Answers: 1. D 2. A 3. D 4. C 5. C 6. D



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