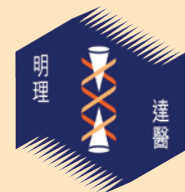


PATHOLOGUE

The Hong Kong College of Pathologists, Incorporated in Hong Kong with Limited Liability



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Message from the President

Pathology is a medical specialty integrating personal experience and cutting-edge techniques. As a professional body committed to the upkeep and assurance of high-quality pathology practices, our College is dedicated to equipping our fellows with the ability to meet the challenges of evolving advancement in techniques and increasing expectation of the community.

Concurring with the initiative by Hong Kong Academy of Medicine to promote training in genetics and genomics in several specialties, our College has been working on establishing a post-specialty fellowship in Genetic and Genomic Pathology under a special task force led by Dr Michael CHAN involving Specialty Board Chairpersons, Chief Examiners and representatives from various pathology specialties. Continued input of opinions from fellows and trainees is important.

We are encouraged by the success of the International Pathology Day Workshops targeted at high school students. The success is attributed to the hard work of a team of young fellows and trainees from various pathology specialties under the leadership of Dr Leon LAI. This year, such a workshop will be conducted again at around 15 November 2017. We shall continue to count on selfless support from fellows and trainees.

The College will continue to enhance communication with overseas and local professional bodies. There are representatives of our College in advisory groups in local administrations, and regular meetings with sister colleges overseas will continue.

The future of the profession and the College lies with our young fellows. The Academy is forming a Young Fellows Chapter for better engagement in the Academy's activities. Each college is asked to nominate one fellow who has been conferred fellowship within the past 10 years. Dr MAK Siu Ming has been nominated to serve the first term (one year) of this Chapter.

The time of succession has also come. Nomination for Office Bearers and Councillors will be open soon. Your active participation is crucial for the success and prosperity of the pathology profession.

*Professor CHEUNG Nga Yin, Annie
President
May 2017*



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President's activities



▲ *Museum of Medical Sciences Fundraising Dinner on 1 November 2016.*



▲ *Meeting with delegates from The Royal College of Pathologists of Australasia on 25 November 2016.*



▲ *Receiving officiating guests at the Conferment Ceremony on 26 November 2016.*



▲ *Dinner with Fellows and guests after the AGM on 26 November 2016.*

Annual General Meeting 2016

The 25th Annual General Meeting (AGM) was held after the 12th Trainee Presentation Session on 26 November 2016. Six Councillors were elected in AGM 2016. Four of them were in previous Council 2015/2016, and they were all re-elected to the same posts in AGM 2016 as follows. Dr SHUM Shui Fung Bobby was re-elected as Vice-President, Dr WONG Lap Gate Michael was re-elected as Honorary Treasurer, Dr CHAN Kui Fat and Dr LO Yee Chi Janice were re-elected as Council Members. Two new Councillors were elected in AGM 2016. Dr LAM Woon Yee Polly and Dr LEUNG Yuk Yan Rock were elected as Council Members to fill the vacancies left behind by Dr IP Pun Ching Philip and Dr LAI Sai Chak.



◀ Office Bearers on stage at the AGM.

▼ The Council. Front row, left to right: Dr MAK Siu Ming, Dr TANG Wai Lun, Dr CHAN Ho Ming, Prof. CHEUNG Nga Yin Annie, Dr SHUM Shui Fung Bobby, Dr WONG Lap Gate Michael. Back row, left to right: Dr LAM Woon Yee Polly, Prof. HO Pak Leung, Dr CHAN Chak Lam Alexander, Dr LO Yee Chi Janice, Dr CHAN Kui Fat. Absent with apologies: Dr LEUNG Yuk Yan Rock, Dr YUEN Yuet Ping, Dr YUEN Wah Fun Nancy.



Conferment Ceremony

In the Conferment Ceremony, 10 Fellows and 9 Members were admitted to the College. The honourable guests included Dr LAU Chor Chiu (Honorary Secretary of the Hong Kong Academy of Medicine), Dr CHUI Tak Yi (Cluster Chief Executive, Kowloon East Cluster, Hospital Authority), Dr Michael HARRISON (President of The Royal College of Pathologists of Australasia) and Professor Tony LANDGREN (Chair, Board of Education & Assessment, The Royal College of Pathologists of Australasia). College President Professor CHEUNG Nga Yin Annie shared with the audience her work during her tenure as the President of the College.



▲ Prof. Annie CHEUNG and Dr LAU Chor Chiu lead the procession of officiating guests.

▼ New Fellows and Members happily waiting for the ceremony to begin.





▲ *Dr CHONG Yeow Kuan.*



▲ *Dr AU Yuen Ling Elaine.*



▲ *Dr CHAK Pui Kwan.*



▲ *Dr CHEUNG Tin Yan Elaine.*



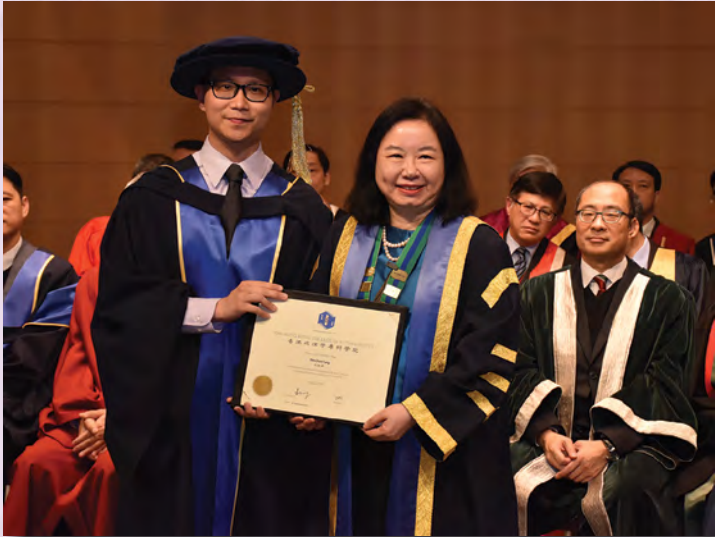
▲ *Dr NG Kwan Shing.*



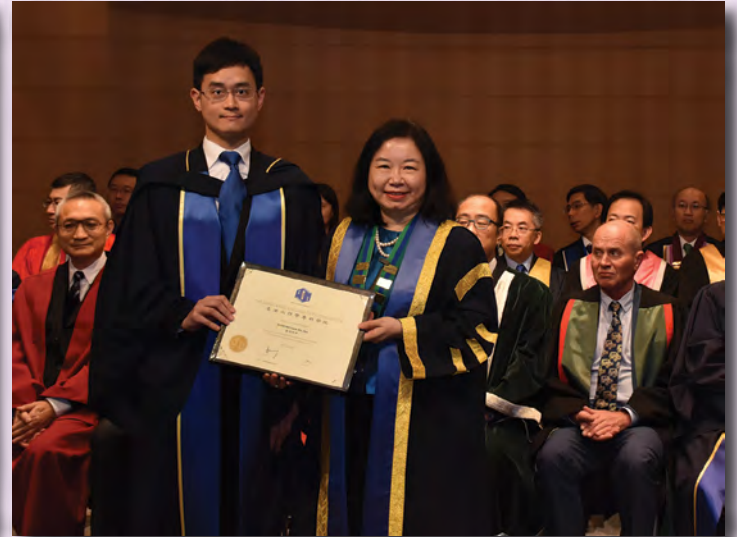
▲ *Dr LOK King Fung.*



▲ *Dr WONG Cheuk Ying Sally.*



▲ *Dr SIN Chun Fung.*



▲ *Dr AU YEUNG Kwok Him Rex.*

Congratulations to the newly admitted Fellows!



▲ *Dr Michael HARRISON delivers a speech.*

▼ *Group photo of Councillors, guests, new Fellows and new Members after the ceremony.*



T.B. Teoh Foundation Lecture

The 25th T.B. Teoh Foundation Lecture was delivered by Dr LEE Kam Cheong, Consultant Pathologist, Department of Pathology, Princess Margaret Hospital. In the lecture titled "Digital Workflow in Anatomical Pathology – On Track to Patient Safety and Beyond", Dr Lee enlightened the audience on the various aspects of digital workflow in anatomical pathology.



▲ *Dr KC LEE delivers the TB Teoh Foundation Lecture.*

► *Prof. Cheung presents a souvenir to Dr Lee.*



We would like to thank Dr Regina LO for being the Mistress of Ceremonies in the AGM. We thank Mr Victor HUNG and Mr Leo YIP for taking photos during the Trainee Presentation Session, AGM, Conferment Ceremony, T.B. Teoh Foundation Lecture and the dinner. We would also like to express our gratitude towards our College Secretary, Ms Adrienne YUNG, as well as Ms Maizie CHAN and Ms Heidi CHU, for their continuous support in organizing the AGM.



▲ Senior pathologists having a nice reunion.

▼ Senior pathologists and guests enjoying an evening at the banquet.





▲ *Younger pathologists also have a good time.*



▲ *What a happy day!*

▶ *Our youngest guest enjoys quality family time.*



**Looking forward to seeing you all
in the coming AGM.**

The 12th Trainee Presentation Session

The 12th Trainee Presentation Session was successfully held in the afternoon on 26 November 2016. Four Fellows in different disciplines were invited to be judges: Dr Eudora CHOW (Haematology, United Christian Hospital), Prof. P.L. HO (Clinical Microbiology & Infection, The University of Hong Kong), Dr Amanda KAN (Anatomical Pathology, Tuen Mun Hospital) and Dr W.T. POON (Chemical Pathology, Pamela Youde Nethersole Eastern Hospital).

The Trainee Presentation Session gives a good platform for our trainees to present their research findings. The response from trainees remains enthusiastic, and this year a total of 16 trainees from different specialties actively participated in the Trainee Presentation Session, either by oral or poster presentation. Both oral and poster presentations are recognized education activities that fulfil the training requirement of our College. Participants of oral and poster presentations had 14 minutes (including 3 minutes Q&A) and 4 minutes (without Q&A session) of on-stage presentation, respectively.

I would like to congratulate all participants for their excellent job and impressive presentation. On behalf of the Education Committee, I would also like to express grateful appreciation to our invited judges and helpers assisting the Trainee Presentation Session.

The best presentation was awarded to Dr Clarice CHEUNG (Forensic Pathology, Department of Health). She presented her study on "Predicting Height of Fatal Fall from Autopsy Findings". The abstract of her study is reproduced below.



▲ Group photo of judges and participants..

Predicting Height of Fatal Fall from Autopsy Findings

Background: Deaths due to falls from height is common in Hong Kong. In some cases, the jumping/falling point could not be located after initial investigations by Police. Height of a fall has been found to correlate with the extent, severity, and specific patterns of injury. A mathematical model was constructed by Lau, Ooi, & Phoon (1998) to estimate height of fatal fall from injuries found at autopsy. However, there was a paucity of data regarding its accuracy and applicability in the local setting.

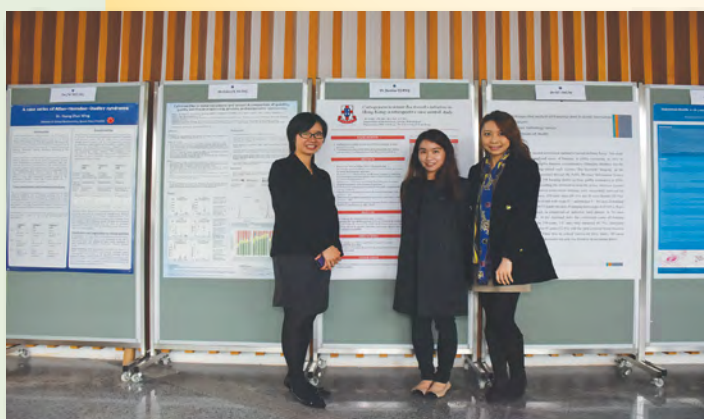
Objectives: (1) To determine the accuracy of using the mathematical model (Lau, Ooi, & Phoon, 1998) to estimate height of fatal fall from autopsy findings. (2) To evaluate the association between height of fall and specific injury patterns.

Methods: This is a retrospective study on fatal falls from height in which medico-legal autopsies were conducted at the three public mortuaries in Hong Kong in year 2013. Corresponding autopsy findings and relevant police reports were reviewed. Autopsy findings were coded according to the Abbreviated Injury Scale 2005: Update 2008, and specific injury patterns analysed.

Results: Of the 100 cases included in the study, age of the deceased ranged from 3 - 93 years (mean 48.31 years). Height of fall ranged from 6 - 67.63 m (mean 36.68 m). The mathematical model accurately predicted the height of fall in 85% cases ($r = 0.881456$, $p\text{-value} < 0.00001$), over-estimating 6 cases and under-estimating 9 cases. Certain specific injury patterns were found to be associated with height of fall. Contrecoup brain contusions were found only in low falls (≤ 30 m). Aortic lacerations and vertebral compression fractures were associated with high falls (≥ 30 m). These associations were consistent with findings in previous studies.

The study by Dr Cheung did not involve any sophisticated genetic or genomic techniques but our judges and I were highly impressed by this outstanding study. Through the presentation, we were convinced that this simple but clinically relevant study was self-initiated and largely (if not solely) completed by Dr Cheung on her own. Although large-scaled studies with complicated high-end research methods are undoubtedly eye-catching, formulation of meaningful research question, planning and implementation of the research by oneself are much more important and valuable for a budding researcher. I am looking forward to seeing more self-initiated studies by our trainees.

Dr Anthony CHAN
Vice-Chairman, Education Committee



▲ Many trainees submitted posters to the Trainee Presentation Session.

► Dr Clarice CHEUNG receives the Best Presentation Award from Dr Anthony CHAN.



TOPICAL UPDATE

Volume 12, Issue 1 January 2017

*The Hong Kong College of Pathologists, Incorporated in
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Editorial note: In this topical update, Dr Rock Leung reviews the testing strategy and quality assurance issues on laboratory testing for direct oral anticoagulant (DOACs). We welcome any feedback or suggestions. Please direct them to Dr Rock Leung (e-mail: leungyyr@ha.org.hk) of Education Committee, The Hong Kong College of Pathologists. Opinions expressed are those of the authors or named individuals, and are not necessarily those of The Hong Kong College of Pathologists.

Laboratory testing for Direct Oral Anticoagulants (DOACs): Are we ready?



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Division of Haematology, Department of Pathology and
Clinical Biochemistry
Queen Mary Hospital, Hong Kong

DOACs	Direct oral anticoagulants
FIIa	Thrombin
PK	Pharmacokinetics
PD	Pharmacodynamics
PT	Prothrombin time
APTT	Activated partial thromboplastin time
TT	Thrombin time
dTT	Diluted thrombin time
ECT	Ecarin clotting time
DRVVT	Diluted Russell's viper venom time

Introduction

The newly available Food and Drug Administration (FDA)-approved oral anticoagulants, namely dabigatran, rivaroxaban, apixaban and edoxaban, have been more commonly used nowadays for treatment and prophylaxis of venous thromboembolism, as well as for prevention of stroke in non-valvular atrial fibrillation.

This new class of anticoagulants has been referred as novel oral anticoagulants (NOACs), target-specific oral anticoagulants (TOACs), or direct oral anticoagulants (DOACs). For the sake of standardization, the International Society for Thrombosis and Haemostasis (ISTH) Scientific and Standardization Committee (SCC) for the control of anticoagulation recommends the term DOACs. DOACs have been shown to be at least as effective as warfarin in various clinical trials. Moreover, there was reduced incidence of intracranial haemorrhage reported in some studies when compared with warfarin [1]. Unlike warfarin, DOACs do not need routine therapeutic monitoring given their predictable pharmacokinetics (PK), pharmacodynamics (PD) and wide therapeutic windows. There are, however, clinical conditions that measurement of anticoagulation activity of DOACs is necessary or potentially useful, e.g. before invasive procedures, during adverse events like break-through bleeding or thrombosis, and pre- and post-administration of reversal therapy for patients with DOACs overdose. Thus, there is a role for laboratory, by testing for DOACs, to help clinicians on patient management. In addition, it is the responsibility of the laboratory to acknowledge

the interferences of DOACs on conventional and special coagulation tests as part of the laboratory quality assurance in the era of gaining popularity of DOACs usage.

Mechanisms of actions of DOACs

In contrast with heparin that can only inhibit free protease, DOACs are rapidly-acting, targetspecific anticoagulants that inhibit both the free and bound activated serine protease [2]. The fact that DOACs can inactivate bound serine protease explains their more robust action than warfarin or heparin. Dabigatran is a direct thrombin (IIa) inhibitor while rivaroxaban, apixaban and edoxaban are direct inhibitors of activated factor X (Xa). Most of the DOACs are cleared by liver and kidney, with the exception of dabigatran being almost exclusively excreted by kidney. DOACs reach peak plasma levels within approximately two hours and plasma trough levels within 12 hours or 24 hours depending on their frequency of administration [3]. The DOACs can be withheld a few days before elective surgery or invasive procedures due to their short half-lives and favourable pharmacokinetics.

To test or not to test?

Routine monitoring of DOACs is not required. Testing on patients on DOACs is generally indicated in certain clinical circumstances, including acute bleeding, suspected DOACs overdose, drug interaction, in patients with impaired renal function, before surgery or invasive procedure in patients who have taken the drug beyond 24 hours and with creatinine clearance of <50 mL/min or with extreme body weight [4]. Recently, more pharmacokinetics and pharmacodynamics data on indications of clinical testing came up. Currently it is recommended that checking of drug-specific peak and trough levels for DOACs should be performed for patients with body mass index (BMI) of >40 kg/m² or weighing over 120 kg [5]. There is currently no consensus on when to test for DOACs activities when these drugs are to be used in women with childbearing potential. One should however note that animals studies have shown teratogenic effect of dabigatran, edoxaban and rivaroxaban, these drugs were assigned by the FDA as pregnancy category C, reflecting their potential teratogenicity. Whereas no teratogenicity has been demonstrated in animals for apixaban as of today, it was categorized as pregnancy category B by FDA [6]. On the other hand, the use of DOACs is considered an off-label clinical application for paediatric thromboembolic diseases [7]. It is not unreasonable to obtain information about anticoagulation activity by laboratory assay for this special group of patients, as in the case of low-molecular-weight heparin (LMWH) usage in select paediatric patients.

Given the predictable pharmacokinetics of DOACs, it was proposed that a pharmacokinetic strategy by stopping the

drug for a time frame adequate for washout of drug effect is safe before surgery or invasive procedures. This approach can only be applied for planned surgery or invasive procedures, with available information regarding patient's renal function as well as the dose and timing of the last DOAC administration. For emergent or unplanned procedures in patients with renal insufficiency or unplanned procedures when the timing of the last DOAC administration is uncertain, measurement of residual drug level will be valuable to assist clinical decisions, including the assessment of bleeding risk and the need for antidote for prompt reversal of DOAC effect before surgery. In life-threatening bleeding associated with the use of DOACs, the measurement of drug level can supplement clinical information to determine whether the bleeding is contributed by the anticoagulation effect of DOACs and whether the administration of DOAC-specific antidotes is required. If antidote is applied, laboratory test can monitor the extent of reversal.

What tests to do?

The ideal test for DOACs shall be accurate, readily available on a 24-hour basis in order to accommodate emergency clinical situations, and with a reasonably short turnaround time (TAT).

Gold standard method using ultra-performance liquid chromatography – tandem mass spectrometry (UPLC-MS/MS) provides the most accurate information about the drug levels for patients on DOACs. However, the test is not readily available in most of the laboratories.

Routine coagulation screening tests, i.e., prothrombin time (PT), activated partial thromboplastin time (APTT) or thrombin time (TT), have been suggested as screening tests for DOACs. For routine coagulation screening tests to be useful and suitable for testing for DOACs, linearity and adequacy of test response to increasing dosage and amenability to standardization are prerequisites [8]. For dabigatran, TT is readily available in most laboratories and prolongation of clotting time is linearly and dose-dependently related to dabigatran concentrations. However, responsiveness is excessive. Therefore, a normal TT should rule out a dabigatran anticoagulant effect but the degree of prolongation poorly reflects drug concentration. Dilute TT (dTT), i.e., testing of TT on diluted plasma, is adequately responsive to dabigatran and suitable for assessment of dabigatran activity. Ecarin clotting time (ECT), using ecarin for the conversion of FII to meizothrombin, to assess anticoagulant effect of dabigatran was also shown to have satisfactory linearity and responsiveness to increasing dabigatran concentrations. APTT, though being demonstrated to have satisfactory responsiveness to dabigatran, lacks linearity upon increasing drug concentration and there is significant

inter-reagent variability ^[9]. PT is insensitive to dabigatran and not suitable for testing.

Rivaroxaban prolongs the PT in a concentration-dependent manner, but the correlation is generally weak and became weaker with increasing drug concentration. Significant reagent-dependent differences in assay sensitivity are noted in multiple studies, limiting its use for assessment of rivaroxaban activity if the in-house thromboplastin reagent for routine coagulation screening is insensitive to rivaroxaban ^[10]. APTT is insensitive to rivaroxaban and shall not be used for assessment of rivaroxaban activity. For apixaban, both PT and APTT are insensitive to increasing drug concentrations and for edoxaban, PT performance is similar to that observed for rivaroxaban and APTT is insensitive ^[11].

Therefore, routine coagulation screening tests PT, APTT and TT cannot provide a reliable measurement of DOAC anticoagulant effect in most circumstances. One exception being a normal TT excludes significant residual effect of dabigatran in patients. Moreover, PT and APTT are either insensitive or show variably sensitivity to the on-therapy range of DOACs and limit their use in determining whether the drug concentration is in subtherapeutic or supratherapeutic ranges. Furthermore, these coagulation screening tests are potentially affected by the presence of lupus anticoagulants and conditions resulting in factor deficiency as in liver disease or dilutional coagulopathy. Thus, the sensitivity & specificity in reflecting the anticoagulant effect of DOACs is limited.

Anti-Xa assay is a chromogenic assay based on the measurement of residual FXa with synthetic substrates upon mixing of plasma with FXa. Although one study showed the feasibility of using of anti-Xa assay for LMWH to assess the presence of rivaroxaban ^[12], it is recommended to use drug-specific calibrator rather than adopting the anti-Xa assay for measurement of heparin activity due to the following reasons: 1) assays to measure indirect Xa inhibitors, e.g., LMWH, are measured in IU/ml and direct Xa DOACs are measured in ng/mL and there is no direct relationship between these two units of measure, 2) there is significant variability in measured drug concentration, as demonstrated by rivaroxaban, between various anti-Xa kits and 3) the therapeutic range, at least for apixaban and rivaroxaban, far exceeds the typical calibration range for UFH and LMWH (in the 5-9 IU/ml range) and 4) the assay is not specific for anti-Xa DOACs and will detect all anti-Xa anticoagulants².

Commercially available drug-specific coagulation assays for testing of DOACs use calibrators and controls specific for the DOAC being measured ^[13-15], enabling the reporting of a drug concentration upon testing of patient's

plasma sample. Multiple calibrators and test plasma dilutions are employed to ensure the test sample responses are within the range of the calibration curve and also to allow for assessment of linearity and parallelism ^[16]. It was recommended that anti-Xa assay and diluted TT shall be employed when carrying out the drug-specific coagulation assay for anti-Xa inhibitor and anti-IIa inhibitor respectively, given their linear relationship and good correlation with drug concentration as measured by mass spectrometry ^[11]. Although an ecarin chromogenic assay (ECA) for direct IIa inhibitor and a DRVVT-based assay for both direct IIa and direct Xa inhibitors have been calibrated for testing of DOACs, ECA was shown to have suboptimal accuracy when compared UPLC-MS/MS and DRVVT-based assay would give false positive result in the presence of lupus anticoagulant ^[17,18]. Studies have shown that various drug-specific coagulation assays differ significantly in quantitation of the DOAC being measured when compared with UPLC-MS/MS in terms of precision and accuracy ^[17].

What is the meaning of drug concentration?

Drug-specific assay is by no means a direct measurement of drug concentration for DOACs. Instead it is an extrapolation of drug concentration by its anticoagulation activity measured by clot-based or chromogenic assay.

Therapeutic ranges of DOACs have not been validated by the manufacturing pharmaceutical companies. Moreover, there is no established range of concentrations associated with bleeding. In clinical use, expected trough and peak concentrations as predicated on prescribed dose and frequency are often taken as a reference during result interpretation of drug levels ^[17] (Table 1).

	Trough (ng/mL)	Peak(ng/mL)
Apixaban 2.5 mg twice daily 10 mg twice daily	20-94 30-412	36-100 122-412
Dabigatran 150 mg twice daily	31-225	64-223
Edoxaban 30 mg once daily 60 mg once daily	130-174 268-336	376-412 388-444
Rivaroxaban 10 mg once daily 20 mg once daily	1-38 4-96	91-195 160-360

▲ **Table 1: 5th – 95th percentile of peak and trough concentrations of DOACs obtained from pharmacokinetic and pharmacodynamics studies on patients prescribed with fixed dose and frequency of DOACs.**

There is no consensus on whether trough level is superior to peak level when interpreting the findings during monitoring of DOACs. The sample for DOAC level is often collected at a random time during emergency clinical situations. A meaningful interpretation of drug level requires the knowledge of the time of last dose of DOAC, the drug dosage and patient's renal and liver functions so that the trend of drug concentration over time can be better predicted.

With increasing use of DOAC assay, it is expected that DOAC plasma concentration shall be a standard study parameter in future clinical trials. This will allow the identification of drug concentration threshold associated with bleeding, the establishment of a therapeutic range for different kinds of DOACs and better definition of DOAC-induced bleeding complications.

Antidote for reversal of DOACs

Non-specific reversal agents like prothrombin complex concentrates, "bypassing agent" like factor eight inhibitor bypass activity (FIBA) and activated FVIIa were used for the correction of DOAC effect. They only had a general antagonizing action on the anticoagulation effect of DOAC without targeting the specific DOACs themselves. Three antidotes for the DOACs are now under various stages of development. Idarucizumab (Praxbind®), the antidote for dabigatran, is now licensed in the United States and recommended for licensing by the European Medicines Agency. Andexanet alfa, the antidote for the oral anti-Xa inhibitors, is undergoing phase III study. Ciraparantag (PER977), an agent reported to reverse the anticoagulant effects of all of the DOACs is at an earlier stage of development [19]. In life-threatening bleeding, administration of antidote or reversal agent before emergency operations shall not be delayed until the availability of test results. Otherwise, the decision on whether antidote is indicated can be guided by suitable laboratory assay as mentioned in the previous section. Drug-specific assay is considered the most suitable candidate given its superior sensitivity and probably better specificity than conventional coagulation assay and better accessibility and faster turnaround compared with mass spectrometry. Measurement of drug activity shall guide the antidote treatment and allow more effective use of this costly medicine. The importance is highlighted by one study on idarucizumab for dabigatran reversal in which dTT was normal on study entry in nearly one quarter of the study population, indicating little or no circulating anticoagulant in this group of patients, whom benefit from the administration of idarucizumab was minimal [20]. Although DOAC concentrations warranting the administration of antidote were recommended (e.g., a drug concentration over 50 ng/mL in serious bleeding and 30 ng/mL in patients requiring urgent intervention) [19], these actionable limits have not been validated in clinical studies.

Quality assurance issues on DOACs testing

Laboratories should develop customized algorithms on DOACs testing strategy for DOACs based on their need. The relative sensitivity of routine coagulation screening test, especially APTT and TT for dabigatran and PT for rivaroxaban, apixaban and edoxaban shall be validated by calibrated materials. Most published algorithms [21, 22] assume patient's coagulation status is solely under the effect of DOACs and may not be applicable for patients with massive transfusion, disseminated intravascular coagulopathy (DIC) or presence of lupus anticoagulant that may have contributed to the abnormal coagulation screening results. Moreover, it is not practical to change the service PT and APTT reagents solely for DOACs detection.

The set up of clot-based or chromogenic drug-specific assay needs careful literature review on the performances of different commercially available assays. For example, one study reported overestimation of rivaroxaban levels with an anti-Xa assay utilizing exogenous antithrombin [23] and ISTH [4] recommended against its use. Nevertheless, the choice of commercially available assay may be limited by its compatibility with the automated coagulometers in service.

There are currently no standards or guidelines on the validation of drug-specific coagulation assays. Same principles on validation for clot-based or chromogenic coagulation assay shall follow, including testing for accuracy, within-run & between-run precisions and lower limit of quantification (LOQ). The testing of accuracy may be limited by accessibility to mass spectrometry. This can be resolved by testing accuracy against different lot of calibrators. Precision at low drug concentration is important to determine any significant residual DOAC effect in emergency setting. Assay kit with incorporation of low-level calibrators is favored over those with calibrators only covering the usual on-therapy concentration ranges. For the same reason, LOQ validation is important and the report shall report results as "less than" numerical LOQ value (ng/mL). Testing on plasma collected from normal subjects not taking DOACs shall be carried out to determine the intrinsic anti-Xa or anti-IIa activity from natural anticoagulant, e.g., antithrombin, which may also affect the lowest reportable limit of the assay.

As part of the quality assurance, PT, APTT, TT and fibrinogen activity shall be assessed for samples sent for quantitation of DOACs. When TT is prolonged, heparin contamination shall be excluded by carrying out protamine neutralization test. Before reporting the drug concentration, linearity of the calibrator curves shall be verified. Calibrator curve shall be acquired for every patient sample instead using stored calibrator curves as a control of lot-to-lot variation of calibrators for this relatively infrequent test. Results shall be

Assay	Anti-FIIa DOAC	Anti-FXa DOAC
Clauss fibrinogen	May be falsely decreased	No effect
One-stage APTT-based factor assays	May demonstrate false decrease in factor activity	May demonstrate false decrease in factor activity
One-stage PT-based factor assays	May demonstrate false decrease in factor activity	May demonstrate false decrease in factor activity
Chromogenic FVIII activity	No effect	May demonstrate false decrease in factor activity
Bethesda assay	False inhibitor present	False inhibitor present
AT activity: thrombin substrate	May demonstrate false increase in AT activity; may mask AT deficiency	No effect
AT activity: FXa substrate	No effect	May demonstrate false increase in AT activity; may mask AT deficiency
PC activity: clot based	May demonstrate false increase in PS activity; may mask PS deficiency	May demonstrate false increase in PC activity; may mask PC deficiency
PC activity: chromogenic	No effect	No effect
PS activity: clot-based	May demonstrate false increase in PS activity; may mask PS deficiency	May demonstrate false increase in PS activity; may mask PS deficiency
PS activity: chromogenic	No effect	No effect
PS activity: ELSA-based or LIA-based	No effect	No effect
LA testing	Possible to misclassify as LA present	Possible to misclassify as LA present
Activated PC resistance	Falsely increased ratio; possible to misclassify as FV Leiden mutation absent	Falsely increased ratio; possible to misclassify as FV Leiden mutation absent

AT, antithrombin; PC, protein C; PS, protein S, LA, lupus anticoagulant; LIA, latex immunoassay

▲ Table 2: Impact of DOACs on select special coagulation assays.

reported in ng/mL, and there should be an accompanied comment about the appropriate range of results (peak or trough levels) based on publication. Drug level shall be interpreted in light of the time since last dose of DOAC intake as well as the dosage of DOAC taken. It is critical to have continuous surveillance of test performance over time. This can be achieved through enrollment in External Quality Assurance Programme (EQAP) (e.g., College of American Pathologists).

Drug-specific coagulation assay can be performed by automated coagulometers with pre-set dilution and analysis protocols with a low to moderate level on skill requirement and hence amenable to the organization of a laboratory-wide staff training programme to cater for the development of a routine 24-hour DOAC laboratory testing service. Interval refreshment training shall be organized to upkeep staff competence. Clinical pathologists shall be involved in communication with clinicians during emergency management of patients requiring DOAC testing to ensure efficient delivery of accurate information to facilitate patient management.

Impact of DOACs on special coagulation assay

It is important for laboratories that carry out special coagulation assay to acknowledge the interferences of DOACs on special coagulation assay. These include clot-based and chromogenic assay. ELISA-based and molecular assays are essentially not affected by DOACs (Table 2) [2,17].

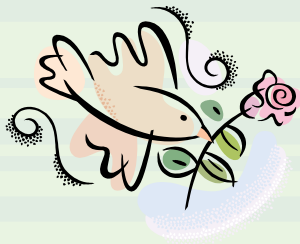
Conclusion

DOACs are more commonly used nowadays. While clinical indications for laboratory testing are more available, there is a pivotal role of laboratories to formulate a testing strategy for DOACs. Routine coagulation screening tests are not informative in most cases. Development of drug-specific assay for DOACs testing is needed. The interpretation of drug level generated by drug-specific assays needs to be facilitated by more data on the association between drug concentrations and bleeding risks expected in future studies.

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OBITUARY – DR JOAN FAOAGALI



Dr Joan FAOAGALI is fondly remembered and sadly missed by our College, especially microbiologists. A number of us first met Joan when she visited Hong Kong as Chief Examiner in Microbiology of the Royal College of Pathologists of Australasia (RCPA). My first impression of Joan was that she meant serious business. She took it upon herself to schedule visits to all RCPA training centres, including those overseas, to ensure the standard of Fellowship of the RCPA.

During her visits to training centres in Hong Kong, she asked probing questions and exhibited a comprehensive and thorough approach to understand the programmes offered to trainees. From 2010 to 2012, we were fortunate to have Joan for three consecutive years in Hong Kong, when she accepted our College's invitation to be External Examiner in Clinical Microbiology and Infection for our Membership examinations and Fellowship assessments. Since my first meeting with Joan, and throughout my liaison with her, I came to admire her strong personality, and her speaking up and standing up for what she believed in. We in Hong Kong are proud and honoured to be associated with Joan. With kind agreement from Joan's family, we have reproduced her valedictory.

Dr Janice LO



▲ A photo taken during the Examiners' Dinner for Clinical Microbiology and Infection in the evening of 29 August 2011: (front row from the left) Dr NG Tak Keung, Prof. Margaret IP, Dr Joan FAOAGALI (External Examiner), Dr Janice LO and Prof. HO Pak Leung; (back row from the left) Dr Raymond LAI and Dr QUE Tak Lun (Chief Examiner).

Joan Lorraine Faoagali Gwynne (nee Wilson) 3/9/1940 - 1/1/2017

Joan was born in Ashburton, New Zealand (NZ), eldest child of Alice and Les Wilson. She had one younger sister and 2 younger brothers. She spent her formative years in Dunedin living in North East Valley, Opoho and Lookout Point.

Joan was educated at North East Valley School which her mother also attended, then Otago Girls High School. She trained as a radiographer at Dunedin Hospital then was accepted in to Otago University medical course in 1960 graduating MBChB in 1966.

Joan married her first husband Malaki Faoagali in 1964, gave birth to their first child Susan. In 1965, following graduation from Otago University, she moved to Invercargill (Kew Hospital) for her intern years.

In 1968 the family including second child Kathryn, travelled by 'banana' boat from Auckland to Samoa. Joan realised quickly that the local doctors were very effective however a skill that was needed was pathology. So the family returned to NZ in 1969 where she took a job as a pathology registrar at Kew hospital and then moved to Dunedin to finish her training and specialised in microbiology so she could also enjoy her growing clinical interests.

In 1974 the family, now joined by children Steven, Anna and Mepi, moved to Christchurch where Joan had been appointed the Director of Microbiology at Christchurch hospital.

In 1977 Joan's husband Malaki was diagnosed with a malignant paravertebral neurological tumour and as he wished to return to Samoa, Joan took leave from work and the family relocated to Samoa until Malaki died in September 1978.

Joan resumed her position back in Christchurch and later met and married anatomical and forensic pathologist James Francis Gwynne (Jim) and had 2 more children, James and Elizabeth.

In 1985 the family relocated to Brisbane following Joan's appointment as Director of Microbiology at the Royal Brisbane hospital.

Joan maintained a strong interest in teaching and learning after graduation. As well as her Fellowship of the Royal College of Pathologists of Australasia (FRCPA) she obtained her Diploma in Clinical Pathology (DCP) from OU and a Diploma in Health Administration (DHA) from Massey University.

In Australia Joan was granted a Fellowship of the Australian Society of Microbiology (FASM) a master of public health (MPH) from UQ and a diploma in health administration from UQ/QUT. She undertook teaching at UQ, QUT, and Griffith University and co-supervised masters and PhD students. She was granted academic appointments at each of these institutions.

Joan also participated in postgraduate pathology teaching in Fiji, and was an external examiner in Sri Lanka, Hong Kong, and Malaysia. She was chief examiner in Micro for the RCPA for 6 years, Queensland representative for the RCPA for 6 years and a member of various RCPA committees, Standards Australia, NPAAC and TGA.

Shortly following the death of her husband Jim in 2010, Joan was diagnosed with breast cancer which responded to chemo and radiation and in 2016 was found to have disseminated bony and liver metastases. She eventually succumbed on 1 January 2017 supported by her family.

Joan's 7 children, 10 grandchildren and 2 great grandchildren all of whom she was very proud, survive her.

Joan lived by the mottos: "if a job is worth doing it is worth doing well", and: "never let the truth get in the way of a good story!"

Joan lived a long life her own way and during her final months her children and grandchildren recorded her oral history for future generations, helped by her cousin Edward who suggested questions and themes.

Vale Joan – travel safely

International Pathology Day Workshop 2016

To be commensurate with the celebration of the ILPP International Pathology Day in November, and to promote public understanding of pathology and pathologists' work, the College organised the International Pathology Day Workshop 2016, on 19-20 November 2016, at University Pathology Building of Queen Mary Hospital.

About 250 secondary school students attended the workshop and learnt about pathology and pathologists' work through interactive laboratory experiments and demonstrations, under guidance by volunteering doctors and medical students.

Four identical sessions were held, each lasting about 3 hours. In each session student participants rotated through stations manned by volunteers from all six pathology disciplines. Feedback was overwhelmingly positive and the commonest comment received was that the students wished the workshop had been longer.

Dr Elaine AU, Dr Ingrid CHEUNG, Dr Esther HUNG, Dr Rosalina IP, Dr Elison KAM, Dr SC LAI, Dr Crystal LAM, Dr Garrick LI, Dr Regina LO, Dr Dr KK MOK, Dr Felix WONG and Dr Michael WONG participated in the organisation of this workshop.



▲ *Students enjoy hands-on experiment and type ABO blood groups.*

► *Students trying to identify the bacteria on the petri dishes.*

▼ *Professor Sophia CHAN Under Secretary for Food and Health, poses for a group photo with the President and the organisers after giving a speech.*

