DAWN® AC

ANTICOAGULATION SOFTWARE

Proceedings of the 9th Annual North American DAWN AC User Group Meeting

20th November 2015

"The meeting was great, a wonderful learning experience"

UCLA Healthcare

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The 9th Annual North American DAWN AC User Group was opened by Maija Sanna, MD & Sheila Naghshineh, MD, Co-Directors AMS, UCLA Healthcare who welcomed all of the delegates to the meeting. An excellent and varied programme of talks had been lined up and summaries of each of the talks are enclosed.

Integration of DAWN AC and EPIC

Esther Camargo-Diaz, Patient Management Coordinator & Shannon Ruiz RN, UCLA Healthcare, Los Angeles

The Anticoagulation Management Service (AMS) at UCLA oversees Department of Medicine patients using Point of Care Testing (POCT), home monitoring, labs and home health agencies. The service accommodates between 1400 and 1500 patients.

Currently, UCLA utilizes Care Connect (EPIC) as their Electronic Health Record (EHR). When EPIC was implemented at UCLA, the AMS team explored how EPIC and DAWN AC could work together. After much debate, an interface was put into place that built a communication between the two systems. It is continuously growing and expanding as it is improved upon.

Prior to the integration between DAWN AC and EPIC, the new patient enrollment forms often had missing information that was necessary to complete the enrollment process in DAWN AC. This led to the staff going back and forth to the physicians to obtain the missing information.

With the introduction of EPIC in 2013, the opportunity arose to digitize the enrollment process, by implementing 'required' fields that doctors had to complete in order to be processed. This in turn greatly improved the time taken to have a patient enrolled into the AMS. The enrollment form is completed within EPIC which interfaces demographic information into DAWN AC as a new patient record. The interface between DAWN AC and EPIC utilizes an 'FYI' flag that is placed into the patients chart in EPIC to indicate that they are currently enrolled with the AMS.

Between 2013 and 2014 there was a 95% decrease in missing information on the enrollment forms, specifically with regards to Low Molecular Weight Heparin (LMWH) allergies, along with similar decreases for risks, target range and start dates. By 2015, all enrollment forms were completed online; however there were still some instances where forms still had missing information.

Further investigation by the AMS identified the expansion of their services, and incorporating satellite clinics, as a possible reason for this increase. New physicians were unaware of the AMS protocol for enrollments. The AMS is planning to meet with new clinics and doctors to go over the protocols and ensure all relevant information is provided for new patients.

In addition to the interface above, the implementation of other interfaces both to and from the DAWN AC system have also seen a number of improvements:

- If there is an FYI flag on the EPIC patient record, the Admissions and Discharge (ADT) interface will automatically notify DAWN AC when a patient enrolled with the AMS is admitted or discharged. When this happens, the patient is automatically taken off 'active' on DAWN and placed on a list view so that the AMS has to physically look at the patient record and see if any action is required by them. The ADT interface also saves time inputting demographics into DAWN AC.
- The INR results interface enables lab results to be pre-populated in DAWN AC against the patient record. Both UCLA labs and results from the satellite clinics all come into DAWN AC through this interface, removing the chance of transcription errors as a result of manual input.
- Once a patient's dose has been authorized in DAWN AC, the Dosing Report/Progress Note interfaces and sends the dose information and associated patient notes from DAWN AC into the EPIC patient record. This ensures the central patient record is always up to date with the latest dosing information and is accessible to whichever HCP/department looks at it.

Moving forward, UCLA AMS would like to see a medications interface between DAWN AC and EPIC that pulls all medications from the patient's central medical record into DAWN AC. Any pertinent interacting medications that need action will provide visibility in DAWN AC of all medications that were entered as new, reconciled, or discontinued in the patient's record in EPIC. For these medication interactions, the patient can then be contacted to be tested sooner or the physician can make an empiric dose adjustment as necessary.

In addition, the AMS would like to see direct email communication between nurses and physicians through DAWN AC to EPIC improving efficiency and removing the requirement to use Microsoft Outlook.

POC supratherapeutic INR management at UCLA

Mahalia Bando LVN, UCLA Healthcare, Los Angeles

The Anticoagulation Management Service (AMS) at UCLA looks after two sets of patients, point of care (POC) patients and non-POC patients.

When the AMS receives critical INRs – defined as an INR over 5 – these patients are immediately prioritised. For non-POC patients the MD and nurse practitioner are emailed and paged so that the patient can be contacted and the high INR addressed immediately.

For POC patients who are in clinic they are seen immediately by the AMS preceptor and their INRs are confirmed with a venepuncture INR. If there is a significant difference between the two INRs (finger-stick and venepuncture) it is referred back to the dosing physician for further instructions and a protocol is in place at the laboratory for contacting the dosing physician should the INR be classed as critical.

During 2013 and 2014, a total of 32,279 INRs were dosed. Of the total number dosed, just above 2% (679) were classed as supratherapeutic. The protocol in place for dosing elevated INRs is based on the recent ACCP guidelines.

In 2013 there were 20 patients that were prescribed Vitamin K for INRs over 10. In 2014 this number was 6 and so had reduced quite considerably.

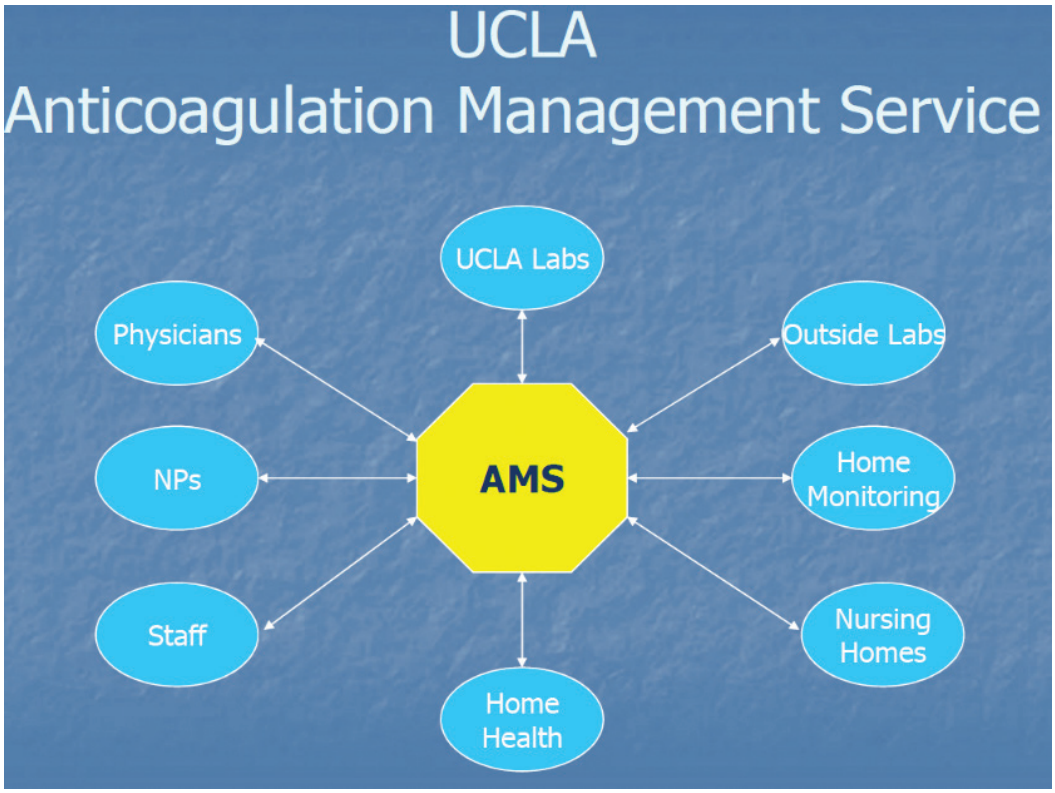
DAWN AC helps the AMS identify and deal with these occurrences:

- Alerts the AMS to investigate the increased INR and the possible reasons for the increase
- Encourages enrolling MDs and AMS preceptors to review patient's history to provide appropriate dosing recommendations.

One of the limitations of the system is that the current set up means that there is no dosing recommendation for high INRs and this throws off the AMS preceptors and enrolling MDs who are not familiar with the software.

However, there are also a number of opportunities for the AMS to use DAWN AC further and these include:

- Coordinate with other providers by utilising DAWN AC and Care Connect to track patient changes
- Continuing education required for both existing and new members of the AMS team
- Continuing patient education and providing access to patient education materials
- The health system is growing and expanding with new satellite clinics
- New anticoagulants coming on board and patients are enquiring about them in terms of how they are being managed and monitored



From: Fish, J. (2010). Use of Pre-visit Patient Questionnaire for Education and Self-Reporting of Adverse Events.

AMS Commitment:
Safe, efficient, evidence-based practices.

Goals:
- Appropriate care
- Manage dosing
- Provide systematic monitoring and patient education
- Provide ongoing education
- Communicate with other providers

Future expectations for the AMS:
- Improved coordination with other healthcare providers system-wide specifically in terms of:
    - Patient health status change
    - Medication changes
    - Preparation for surgery
- Coordination with other departments and offices who provide the same service within the health system, for patient safety purposes.
- Continuing education opportunities offered and implemented for team members
- Uniform and standard health teaching materials and information for patients

Warfarin as a new anticoagulant – improving stability and outcome of warfarin by monitoring factors II and X only

Dr Pàll Önundarson, MD, Landspitali Hospital, Iceland

Dr Önundarson discussed the results of his Fiix-PT trial which aimed to assess non-inferiority of anticoagulation stabilisation with a warfarin monitoring method affected only by factors II and X (Fiix-prothrombin time [Fiix-PT]) compared with standard PT-INR monitoring that includes factor VII measurement as well (and factors I and V).

Whilst warfarin is very efficacious, the efficacy of VKA depends heavily on the quality of warfarin management. Between 1985 and 2014 there has been a marked improvement in warfarin control in the Western world, from the introduction of international standardisation of prothrombin time (PT) reporting (the INR) to anticoagulation management centres with specialised staff; computer assisted dosing; and self-monitoring.

Despite its effectiveness, warfarin still has a number of pros and cons:

Pros	Cons

• Well studied and efficacious
• Controllable anticoagulation intensity by monitoring
  • Therapeutic window is well delineated
  • Adjustable to personal needs (titratability)
• Compliance is measurable
• Immediately reversible
  • Immediately with PPC
  • Hours (FFP)
  • 12-16 hours vitamin K
• Cheap
	• Slow onset of effect
	• Hard to predict initial dose
	  • Mutations affect metabolism and dose size
	  • VKORC
	  • CYP450
	• PT-INR fluctuates
	  • In many patients leading to need for frequent testing and dose adjustments
	• Serious bleeding complications
	• Needlestick
	• Work!

So can warfarin treatment be improved further in 2015? Managing warfarin is not easy as doses vary between patients and more importantly, the measured effect fluctuates. This measured fluctuation is often due to food interactions, drug interactions or compliance problems; but could test problems (the PT itself) misrepresent the anticoagulation in a patient and lead to a fluctuating effect?

A number of studies have suggested that the PT-INR is not a great indicator of the antithrombotic effect of VKA and that the antithrombotic effect depends mainly on reductions in FII and FX:

- **Thrombin generation correlates with FII and less with FX but poorly with factors VII and IX activity.** *Xi M,* Béguin S, Hemker HC. Thromb Haemost. 1989 Sep 29;62:788-91;
- **Induced DIC in rabbits is prevented by reduced FII and FX but not by reduced FVII.** *A Zivelin, LV Rao and SI Rapaport. J. Clin. Invest. 92: 2131-2140 (1993);*
- **Monitoring warfarin with NPA. Monitoring native FII lead to 85% reduction in major events compared to PT monitoring.** *Furie B, Diuguid CF, Jacobs M, Diuguid DL, Furie BC. Blood. 1990; 75:344-9;*
- **ROTEM experiments with low TF concentration.** *Gudmundsdottir BR, Francis CW, Bjornsdottir A, Nellbring M, Onundarson PT. Thromb Res 2012;130:674–81.*

Based on these results a hypothesis was formed:

'During VKA anticoagulation, measuring the combined influence of only the stable FII and FX reflects clottability better than does the PT-INR which is affected also by the short half-life FVII that has little influence on thrombus prevention but confounds VKA dosing'

Fiix-PT: "Fiixing" the prothrombin time

A modified PT was developed that is only influenced by factors II and X (FIIX). Subsequently a randomized blinded clinical trial was designed and conducted at the Landspitali in Reykjavik.

Design

- Single Center Prospective RCT
  - investigator initiated
  - randomized double blind study
  - non-inferiority trial 2012-2014
  - Landspitali AMS in Reykjavik
- All patients on warfarin with INR target 2-3 > 18 yo invited to participate
  - only exclusions: nursing home patients, cardioversion patients
  - ¾ had atrial fibrillation
- Randomized to monitoring with:
  - Fiix-PT/INR ("Fiix-warfarin")

    - active arm
  - PT/INR ("PT-warfarin")

    - control arm
- A blinded research INR was reported
- Warfarin management
  - specialized nursing staff
  - DAWN anticoagulation software
  - dosing protocol designed for the PT-INR *(with maximum recommended interval 42 days)*

Endpoints

- Efficacy
  - Total thromboembolism
    - Ischemic stroke *(not haemorrhagic stroke)*
    - TIA
    - Systemic arterial embolism
    - Myocardial infarction
    - VTE
- Safety
  - Major bleeding *(ISTH criteria)*
  - Other clinically relevant bleeding
  - Non-vascular death
- Composite major vascular events
- Surrogate efficacy/convenience parameters
  - Number of tests and tests in range
  - Dose change frequency
  - TTR *(Time within target range)*
  - VGR *(variance growth rate; INR fluctuation)*

1,148 patients were randomised for inclusion in the trial, with 573 assigned to the Fiix-PT/INR monitoring arm and 575 to the PT/INR arm. The median observation time was 1.7 years.

The efficacy of Fiix-PT monitoring (or thromboembolic rate) was non-inferior to PT monitoring with an annual rate of thromboembolism of 1.2% in the Fiix-PT arm versus 2.3% in the PT arm.

Whilst the major vascular event rate was similar in the first 6 months, after this time period the difference between the two monitoring arms became much more substantial, in favour of Fiix-PT monitoring with a 50% reduction in thromboembolism rate and the long-term improvement statistically significant.

The primary analysis of clinical outcomes is shown in the table below:

Surrogate efficacy endpoints showed that anticoagulation monitored with Fiix-PT was more stable as evident by a lower variance growth rate (VGR; a fluctuation indicator), higher TTR and fewer dose changes than in patients monitored with the traditional PT.

	Fiix-PT group		PT group		Relative risk (95% CI)	p value for total events†
	n	Percentage per patient observation year*	n	Percentage per patient observation year*		
Primary endpoints						
Efficacy						
Primary outcome population	573	..	575	..		
Total observation years	828	100%	835	100%		
Fatal and first non-fatal thromboembolism including myocardial infarction	10 (1)	1·21% (0·12)	19 (3)	2·28% (0·36%)	0·52 (0·25–1·13)	<0·0001
Cerebral infarction or transient ischaemic attacks	9 (0)	1·09%	14 (1)	1·68% (0·12%)	0·65 (0·28–1·48)	0·0002
Cerebral infarction	7 (0)	0·85%	11 (0)	1·31%	0·64 (0·25–1·64)	0·0002
Transient ischaemic attack	2 (0)	0·24%	3 (0)	0·36%	0·67 (0·11–3·99)	0·0001
Myocardial infarction	1 (1)	0·12%	3 (2)	0·36% (0·24)	0·33 (0·03–3·21)	<0·0001
Peripheral arterial occlusion	0	0	1 (0)	0·12% (0)	..	..
Venous thromboembolism	0	0	1 (0)	0·12% (0)	..	..
Safety endpoints						
Per-protocol population	571	..	573	..	..	..
Total observation years	771	100%	786	100%	..	..
First major bleeding	17 (1)	2·20% (0·13%)	20 (3)	2·5% (0·38%)	0·85 (0·45–1·61)	0·0034
Gastrointestinal	12 (1)	1·56% (0·13%)	10 (0)	1·27% (0)	1·2 (0·52–2·76)	0·0093
Intracranial	2 (0)	0·26% (0)	5 (1)	0·64% (0·13%)	0·4 (0·08–2·06)	<0·0001
Intracerebral	1 (0)	0·13% (0)	3 (1)	0·38% (0·13%)	0·33 (0·03–3·21)	<0·0001
Other major bleeding	3 (0)	0·39% (0)	4 (2)	0·51% (0·25%)	0·75 (0·17–3·35)	0·0002
Non-major clinically relevant bleeding						
All (including repeated)	118	14·25%	135	16·16%	0·88 (0·71–1·09)	0·0140
First non-major clinically relevant bleeding	87	10·51%	95	11·38%	0·92 (0·7–1·2)	0·0379
Minor bleeding	279	36·70%	301	36·05%	0·93 (0·83–1·04)	0·0185
Secondary endpoints						
Death from any cause	12	1·45%	16	1·92%	0·75 (0·36–1·58)	0·0008
Non-vascular death	10	1·21%	10	1·20%	1 (0·42–2·39)	0·0027
Composite major vascular events	27 (2)	3·50% (0·26%)	39 (6)	4·96% (0·76%)	0·69 (0·43–1·12)	0·0006

Non-inferiority analysis of total major events occurring during days 1–720 from randomisation. Fatal events are shown in parentheses. Efficacy of the monitoring method is assessed based on intention-to-monitor analysis, but safety of monitoring method is based on actual time on warfarin including a 5-day washout period after warfarin discontinuation (per-protocol population). Fiix-PT=Fiix-prothrombin time. PT=prothrombin time. *Percentage with event per patient observation year. †p value by Farrington-Manning test of non-inferiority with a non-inferiority margin of 0·025.

Table 2: Primary analysis of clinical outcome

Conclusions:

Compared to high quality (TTR 80%) PT-warfarin, Fiix-warfarin:

- **Is more stable**
- **Is clinically at least non-inferior** (primary analysis)
- **Is clinically superior in the long-term** (secondary analysis)
    - Long-term reduction in thromboembolic events
- **Does not increase bleeding**

Overall conclusion:

- A fluctuating PT-INR during warfarin treatment is partly a confounding side effect of the PT itself.
- The data suggests that if the PT is replaced with a monitoring test that is not affected by FVII such as the Fiix-PT, warfarin becomes more stable than previously assumed; a new oral anticoagulant!

DAWN AC Medication Interface with EPIC and its Benefits

Sally Stansbury, PharmD, Brigham & Women's Hospital (BWH), Boston, Massachusetts, USA

BWH Anticoagulation Management Service (AMS) currently has 3,300 outpatients and is primarily a phone-based service. With ten pharmacists on staff and four pharmacy student interns, there are around 400 patients per pharmacist. 7,000 INRs are dosed and 250 new patients are enrolled every month.

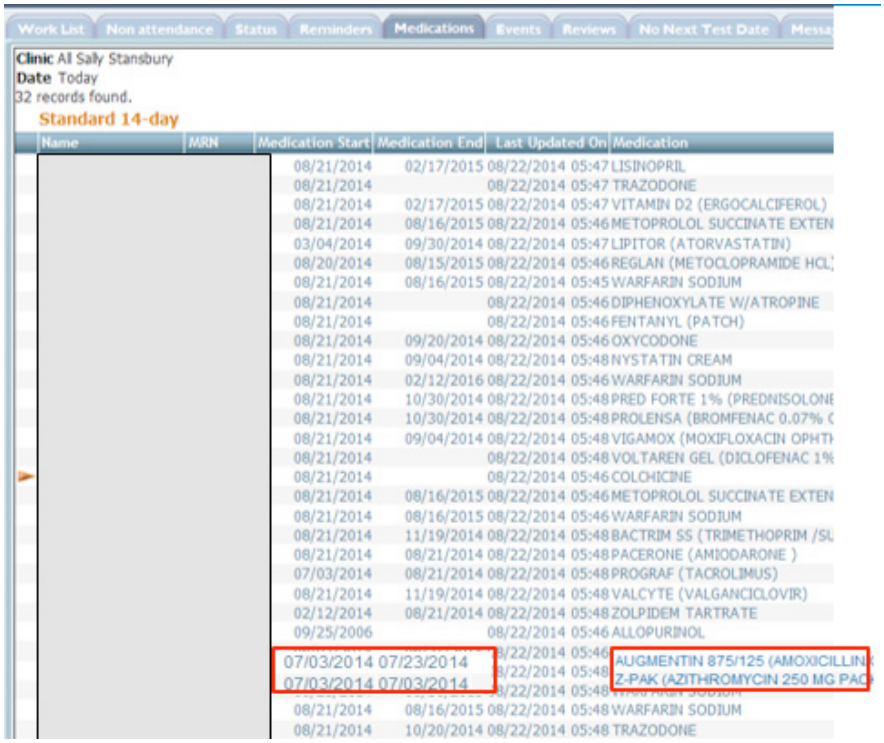
Due to the number of outpatients, there are a number of interfaces in place that keep the AMS staff and other healthcare professionals (HCPs) informed and up to date with important patient information.

The first interface is the AMS icon on the patient record in EPIC. The presence of this icon on the EPIC patient record indicates to the HCP that the patient is under the care of the AMS. When the icon is selected it brings up a review of the patient's anticoagulation, pulled from DAWN AC. This information includes dose history, most recent patient notes and other important information about the patient's anticoagulation treatment.

The laboratory interface is the second interface that the AMS has and this pulls patient INR results from 10 affiliate hospital labs in the Boston area and also from other clinic locations across Massachusetts. This is a particularly helpful interface that reduces transcription errors tremendously. The interface also highlights in DAWN AC which clinic location the INR result has come from and this is shown in the treatment notes.

An EMPI Demographics interface pulls in updated patient information from the Master Patient Index into DAWN AC. This ensures that the patient information held in DAWN AC is always the most up to date available.

In 2014, BWH AMS asked DAWN to create a medications interface that pulls all medications from the patient's central medical record into DAWN AC and there have been many improvements in patient safety as a result. Each night DAWN AC pulls in all of the medications that were entered as new, reconciled, or discontinued in the patient's online medical record within the past day.



The medication tab is checked in the DAWN AC list view daily to see if there are any pertinent interacting medications that need action. This interface provides a huge safety benefit and for these medication interactions, the patient can now be contacted to have them tested sooner or make empiric dose adjustments. Prior to the interface the AMS relied on patients or doctors contacting them with medication changes. The interface also highlights any drug changes to the patients profile within the DAWN AC patient record by highlighting the Drugs tab and recording the changes within it.

A code was set up so that the AMS could determine how many times they have acted on medication notifications specifically from DAWN AC. In one year there were 600 occasions (around 50 per month) which is a significant amount and further emphasises the safety perspective of the interface.

There are a few things that could pose possible obstacles to the new drug interface, including empirically making dose changes too aggressive, causing the INR to become subtherapeutic or supratherapeutic. This can be prevented by making sure to test more frequently when making dose adjustments due to drug interactions. Another issue that may arise is that patients may assume all drugs they are started on will be updated by the interface. This could lead to a decrease in communication from the patient and they may stop reporting new medication changes/dose changes and so it is important to continue to educate patients to take an active role in their healthcare. They need to be reminded to keep their warfarin manager up to date with any medication changes.

In summary, DAWN AC allows for documentation and workflow that is specific to anticoagulation and the interfaces enable transparency throughout all institutions which is a huge safety benefit. In terms of moving forward there are a number of areas that the AMS would like to focus on:

- Integrate Televox which would automate all of the AMS's reminder calls
- Incorporate more labs into the laboratory interface (i.e. Alere)
- Produce a drug-to-drug interaction guideline
- Add more detailed interaction information into DAWN AC to help give more guidance for making empiric dosing decisions
- Enhance communication by setting up text messaging/SMS and email tools through DAWN AC

Time in therapeutic range in geriatric versus non-geriatric population, and geriatric specific AC concerns

Maija Sanna, MD & Sheila Naghshineh, MD, Co-Directors AMS, UCLA Healthcare, Los Angeles, California, USA

Cardiovascular indications for anticoagulation are common in older adults:

- Nonvalvular atrial fibrillation
- Cardioembolic stroke
- Valvular heart disease and prosthetic heart valves
- Severe left ventricular dysfunction
- Venous thromboembolic disease (DVT/PE)
- Peripheral artery disease

Case Example:

- 86 year old female with HTN, HLD, CAD, CKD and mild cognitive impairment recently discharged from hospital after a new diagnosis of atrial fibrillation.
- Patient lives alone, does not drive and manages her own medications. She is widowed, does not have any children but has a neighbour who helps her with grocery shopping. She ambulates with a walker. She has had 3 falls in the past year.
- Her medications include lisinopril and metoprolol, atorvastatin, asa 81 and the newly prescribed warfarin at 5mg.
- Her INR was 2.7 on discharge 4 days ago
- She now presents to the anticoagulation clinic for her initial appointment. Her INR is 1.3.

What are the concerns about this patient?

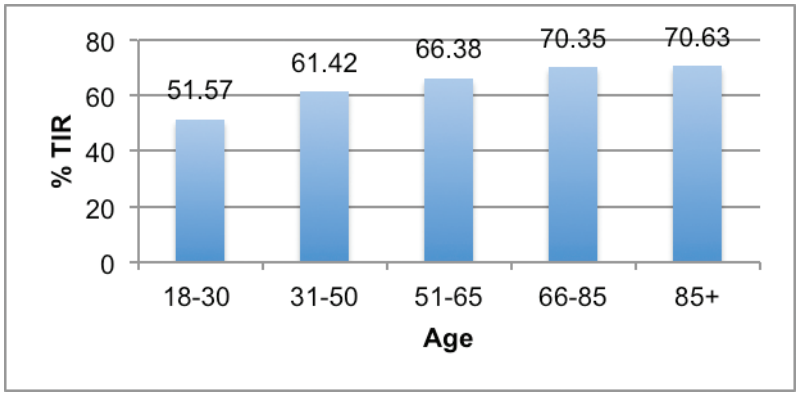
- Fall risk
- Non-adherence (skipped doses/double doses)
- Capacity to understand treatment benefit and risks
- Dual blood thinner risk (aspirin and Coumadin)
- Co-morbidities (uncontrolled HTN)
- Subtherapeutic
- Accurate medication reconciliation (other medications not listed i.e. herbals/vitamins?)

Geriatric specific anticoagulation concerns:

- Polypharmacy and drug-drug interactions. Older people tend to have more medical issues and therefore are prescribed more medications meaning drug-drug interactions are more likely.
    - Medications that increase INR
    - Medications that decrease INR
    - Concurrent use of anti-platelets & NSAIDs
- Cognitive impairments
    - Incorrect dosing
    - Missed pills/double doses
    - Dietary non-compliance
    - Non-compliance to follow-up INR visits
- Poor Diet/Malnutrition
    - Some patients can't afford food or 3 meals a day due to socio-economic factors
    - Comorbid conditions can impact a patients diet as they can restrict what the patient can eat
    - Cognitive conditions such as dementia mean that patients can forget to eat
- Comorbid disease
    - Recurrent falls and subdural hematoma
      Patients with an average risk of stroke (5%/yr without anticoagulation) would have to fall 300 times/year for the risk of anticoagulation related subdurals to outweigh the benefit of stroke prevention[1]
    - Intracranial Hemorrhage (ICH) and hypertension
      Risk factors for ICH included age >75, HTN: SBP>160, hx of cerebrovascular disease, intensity of anticoagulation[2]
    - GI bleeding risk and NSAIDs/aspirin

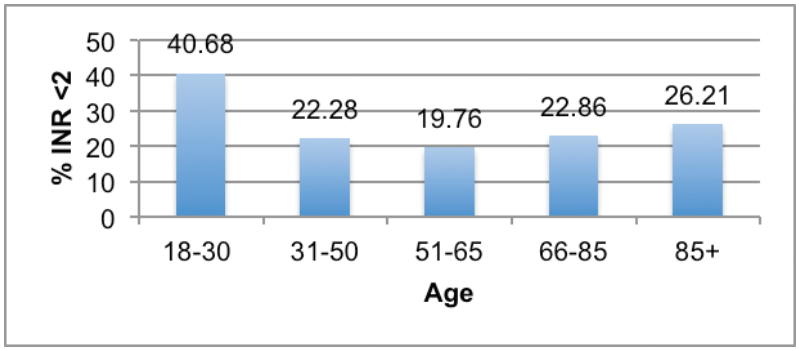
The UCLA AMS team looked into their patient population to compare the data between geriatric and non-geriatric cohorts.

1. Percent Therapeutic Time in Range (TIR) for Non-Geriatric vs Geriatric Patients at UCLA



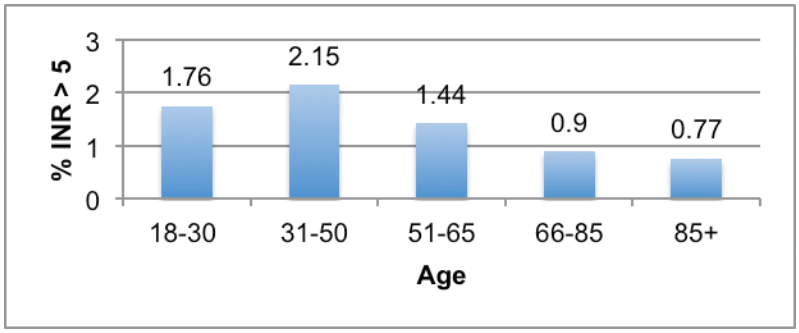
You can see from the graph that the older population have a higher %TIR than the younger population which is the opposite of what the UCLA AMS team expected to find.

2. Percent INR <2 for Non-Geriatric vs Geriatric Patients at UCLA



This graph shows that the younger population had a higher percentage of INRs less than 2, performing less well than the older population.

3. Percent INR >5 for Non-Geriatric vs Geriatric Patients at UCLA

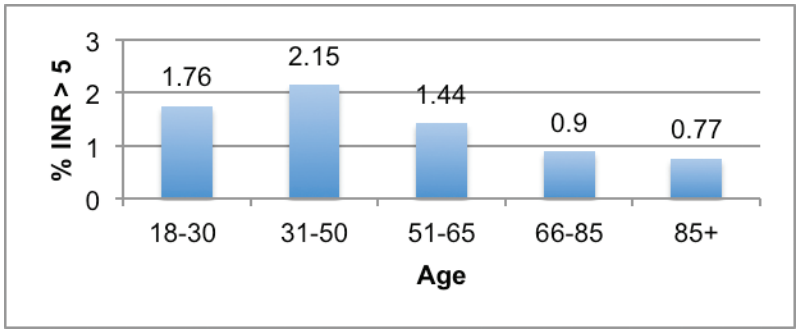


In terms of the percentage of INRs greater than 5, more of the younger population had supratherapeutic INRs than the older population, again surprising the AMS team.

Due to these unexpected results, the AMS team looked at the POC vs non-POC figures for the patient population. These showed that a higher %TIR was achieved with POC testing.

However, specifically in the 18-30 year old cohort, this was not the case and the higher %TIR was achieved with non-POC testing (see Graph 4 below).

4. POC vs non-POC TIR for younger population (ages 18-30)



UCLA Data Summary of Findings

- Geriatric patients spent more time in range than younger patients
    - 71% ages 65+ compared to 52% ages 18-30
- The youngest patients were more frequently in the subtherapeutic time range (INR <2)

    - 41% ages 18-30 compared to 20-26% for ages 31+
- Supratherapeutic INRs were less frequent in the older population
    - 0.8% in patients 65+ compared to 2.15 for ages 31-50
- The youngest patients (18-30) had higher %TIR with non-POC testing (62%) vs POC testing (41%)

Further to the findings, it was clear that the Non-Geriatric population also had adherence issues, although these are quite different from the Geriatric population:

- Priorities (work/school)
- Interruptions in follow up (travel/exams)
- Higher rate of alcohol/drug misuse/abuse (binge drinking)
- 'Invincibility' (perception of youth/health)
- Dietary indiscretions

Solutions to improving %TIR across the entire patient population were derived from the findings of the research:

Patient Population	Solution
All Patients	• Medication reconciliation and MD limit polypharmacy • Education about diet, substance/alcohol use and alternative medications • Improve transition of care (i.e. from ER/hospital to outpatient and nursing home) • Customise to the capability and needs of the patient: non-POC vs POC o 18-30: non-POC provides more flexibility and may increase adherence to INR testing o >31: POC resulted in higher %TIR possibly due to increased adherence vs more receptive to counselling and education
<65 years old	• Set timer or alternative reminder methods for meds/appts • Motivational interviewing to change behaviour (esp. 18-30 year olds)
>65 years old	• Brown-bag all meds to doctor visits/pharmacy to ensure accurate medication list • Caregiver involvement (i.e. fill pill-box, monitoring diet)

In summary:

- The need for anticoagulation is common in the geriatric population
- Comorbid conditions, polypharmacy, cognitive impairment and falls may increase risk of complications
- The benefit of anticoagulation often outweighs the risks in this population
- UCLA geriatric have a higher %TIR vs the younger population
- Be creative and customise anticoagulation management to the patient's needs, capacity and resources

References:
1. Man-Son-Hing et al Arch Intern Med 2003
2. Hart et al. Stroke 2005

Use of Novel Oral Anticoagulants (NOACs) and the new DAWN AC modules at Scripps

Cheryl Ea, PharmD, Scripps Clinic & Scripps Green Hospital, La Jolla, California, USA

The Anticoagulation Service (AS) at Scripps Healthcare is pharmacist managed and their role at Scripps as anticoagulation specialists includes NOAC management. Scripps AS use the DAWN AC NOAC modules for the initiation and follow-up of patients on Apixaban, Rivaroxaban and Dabigatran and out of the 2800 patients enrolled in the AS, around 450 of them are on NOACs. Patients are referred to the AS by outpatient physicians, inpatient physicians and urgent care.

The pharmacist's role in managing NOAC patients is:

- Encouraging adherence
- Adjusting drug dose and following-up renal function
- Identifying adverse drug reactions
- Communicating pre-and-post op therapy instructions
- Following up bleeding complications
- Tracking drug discontinuation and transitioning patients back to warfarin

Non-adherence to NOACs is a concern during long-term anticoagulation. Whilst rates of non-adherence to VKAs have been reported of between 22-58% (Kimmel SE, et al.(1), Van der Meer FJ, et al.(2), adherence to NOACs has been poorly documented and may prove to be an issue now that the drugs are used more frequently outside of clinical trials.

So what information is available from NOAC clinical trials regarding adherence?

- **Einstein PE:** adherence was >80% in 94.2% of patients treated with rivaroxaban (Xarelto)(3)
- **Amplify (DVT & PE):** adherence was >80% in 96% of patients treated with apixaban (Eliquis)(4)
- **Adherence to Dabigatran Therapy in Longitudinal Veterans Administration Cohort:** Distribution of Proportion of days covered across study cohort. Patients with PDC <80% were classified as non-adherent. Patients with PDC ≤80% were classified as adherent. (5)

Scripps AS use the DAWN AC modules for Apixaban, Rivaroxaban and Dabigatran and all three are prescribed for indications of Non-valvular atrial fibrillation and the treatment and prevention of DVT/PE.

The NOAC modules are used to help the AS manage NOAC patients all in one place. As they are integrated into the DAWN AC patient record, the patient's full anticoagulation history is provided.

The modules also enable the AS to ensure that patients are on the appropriate drug and dose, schedule follow-ups, manage missed appointments, report on the NOAC patient population and audit the system.

The AS workflow within DAWN AC for NOAC patients comprises the following:

- Complete an initiation questionnaire
- Stop any existing treatment plan
- Activate a new treatment plan for the chosen anticoagulant and dose
- Schedule a follow-up date for the patient.

The AS manage NOAC patients using specific forms set up as questionnaires (initiation questionnaire and follow-up questionnaire) and these enable the AS to identify valid indications; identify contraindications, identify haemorrhagic risks; advise on dose; check drug and dose are still appropriate; check compliance; and check creatinine clearance among other key information such as HASBLED and CHA2DS-2VASc scores.

After initiation onto a NOAC, the first follow-up is done after 7 days with subsequent follow-ups done at 2 weeks, 1 month and then every 3 months thereafter, dependent upon the patient.

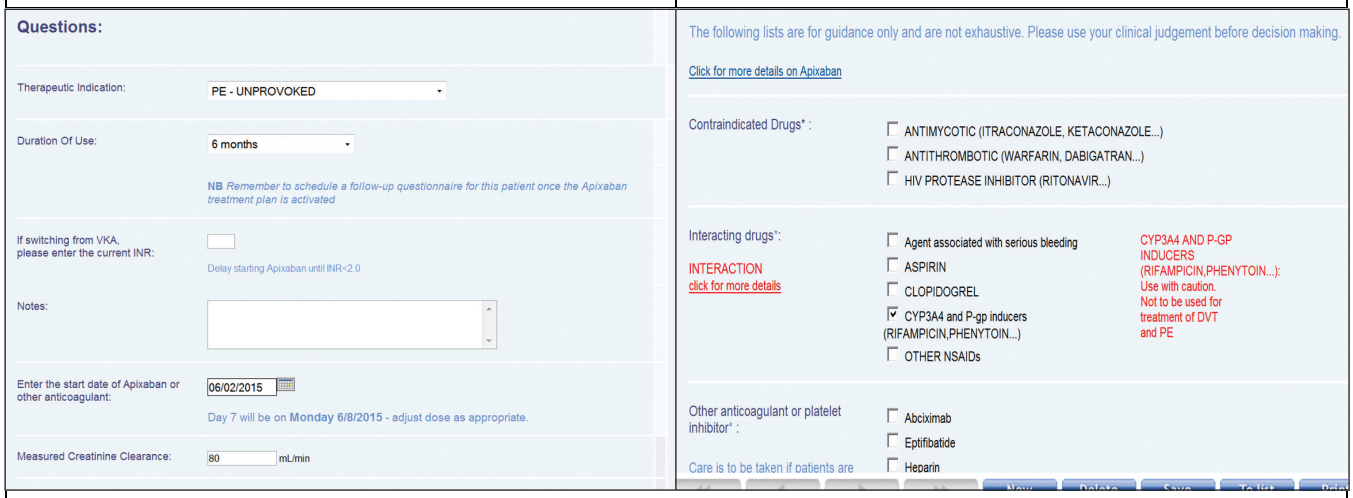
The following examples of two patients seen by the AS show how the DAWN NOAC modules have helped them determine suitability of NOAC and appropriate dose, both at initiation and follow-up stage.

CASE 1

66yo male referred from Urgent Care for acute unprovoked PE/DVT. Patient was given one dose of Lovenox and prescribed apixaban 10mg BID x 7 days then apixaban 5mg BID.

PMH: CAD, HTN, HPL, H/O seizures
Labs: CMP unremarkable, CBC normal, INR=1.0, Scr=0.9
Meds: atorvastatin, omeprazole, phenytoin and vit D

Start of Initiation questionnaire:	*Contraindicated and interacting drugs section:*

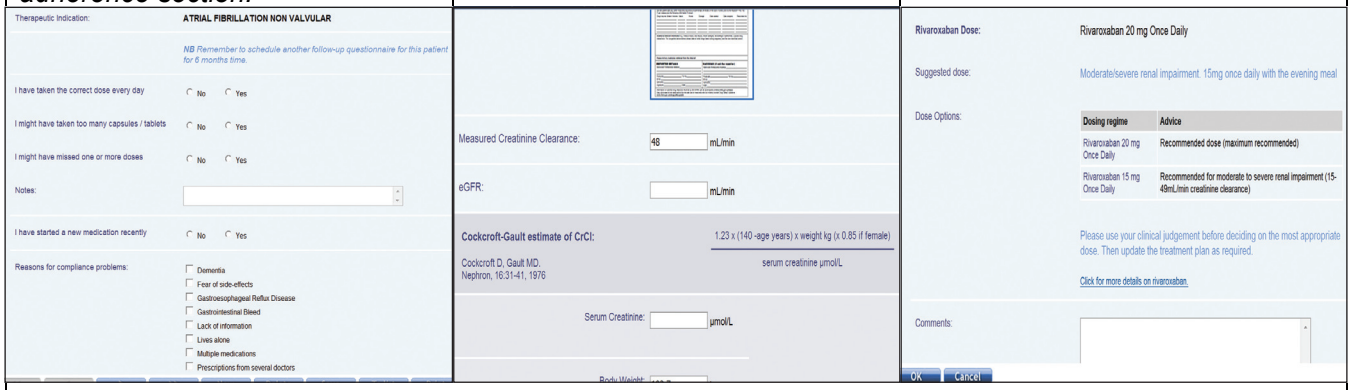


Due to the drug interaction highlighted in the DAWN NOAC questionnaire and the warning not to be used for treatment of DVT/PE, the patient was stopped on Apixaban and transferred to Dabigatran.

CASE 2

73 yo female on Xarelto 20mg qpm for atrial fibrillation due for follow up.
Patient has been having borderline CRCL around 51 ml/min. Upon checking current SCR at follow-up, CRCL = 48 ml/min.

Follow-up questionnaire, adherence section:	*Creatinine clearance check:*	*Suggested dose / dose advice:*



Due to the change in creatinine clearance picked up at the follow-up appointment and added to the questionnaire, the patient's Rivaroxaban dose was adjusted accordingly in the module's dosing advice to take into account the highlighted renal impairment

Due to the incorporation of NOACs into the AS at Scripps, the service is changing from a traditional Coumadin Clinic and is striving to become a multi-disciplinary, comprehensive anti-thrombosis centre, managing thrombotic disease and coordinating all antithrombotic therapy (6).

This comprehensive new Scripps Anticoagulation Service includes:

- NOACs incorporated into the scope of practice
- Development of expertise in the full range of antithrombotic agents
- Peri-procedural management
- Transition between agents
- Drug-drug interactions
- Compliance management
- Knowledge of intervention to avoid or minimise complications and maximise efficacy of therapy

References:
1. Kimmel SE, et al., The influence of patient adherence on anticoagulation control with warfarin: results from the International Normalized Ratio Adherence and Genetics (IN-RANGE) study. Arch Intern Med 2007; 167: 229-35.
2. Van der Meer FJ, et al., The role of compliance as a cause of instability in oral anticoagulant therapy. Br J Haematology 1997; 98: 893-900. 3
3. The EINSTEIN-PE Investigators, N Engl J Med, 2012; 366:1287-97
4. Agnelli, G. and AMPLIFY Investigators., N Engl J Med 2012; 368: 699-708
5. Shore, S., et al., Am Heart J 2014; 167: 810-17
6. Edith A. Nutescu, Pharm.D, et.al., Transitioning from traditional to novel anticoagulants: the impact of oral direct thrombin inhibitors on anticoagulation management. Pharmacotherapy 2004; 24: 199S-202S.

DAWN AC new product developments – DAWN INR Capture: a new web-based service for self-testers & SMS/text messaging from DAWN AC

Alistair Stewart, 4S DAWN Clinical Software

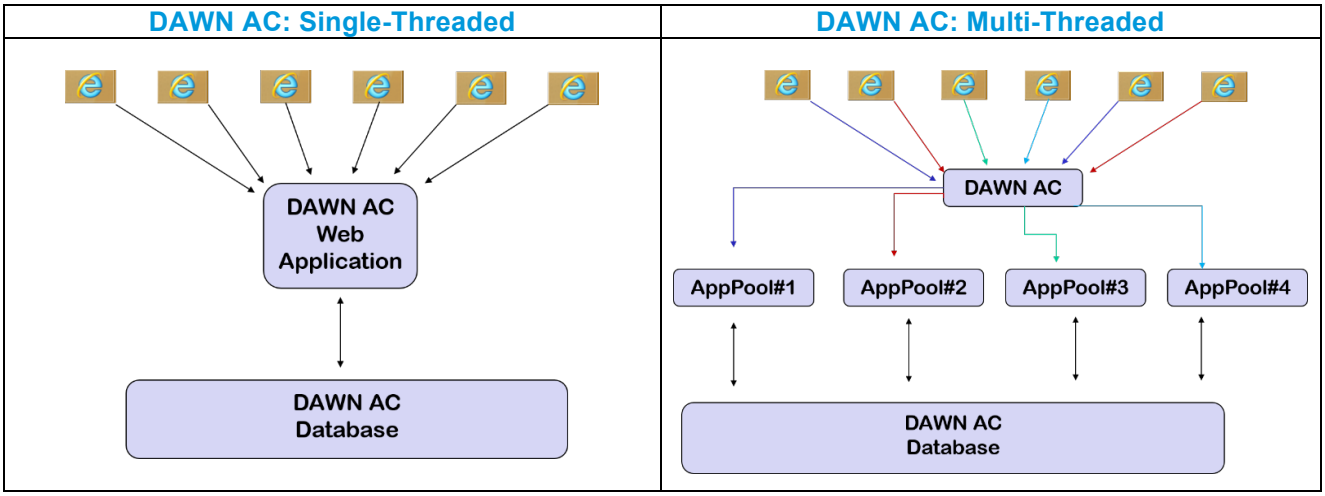
4S DAWN Clinical Software are committed to the continuous development of the DAWN system. A number of new developments have been made within the DAWN AC product over the last twelve months both from a safety perspective and to improve workflows and the usability of the software, providing a range of tools and functionality.

The developments are made up of improvements to existing functionality and the addition of new features into the product.

Load Balanced Application Pools

DAWN AC has historically been a 'single-threaded' application, which means there is one channel of communication between the software program and the database. This means that with multiple users logged in, their actions and requests queue up to be executed sequentially against the database.

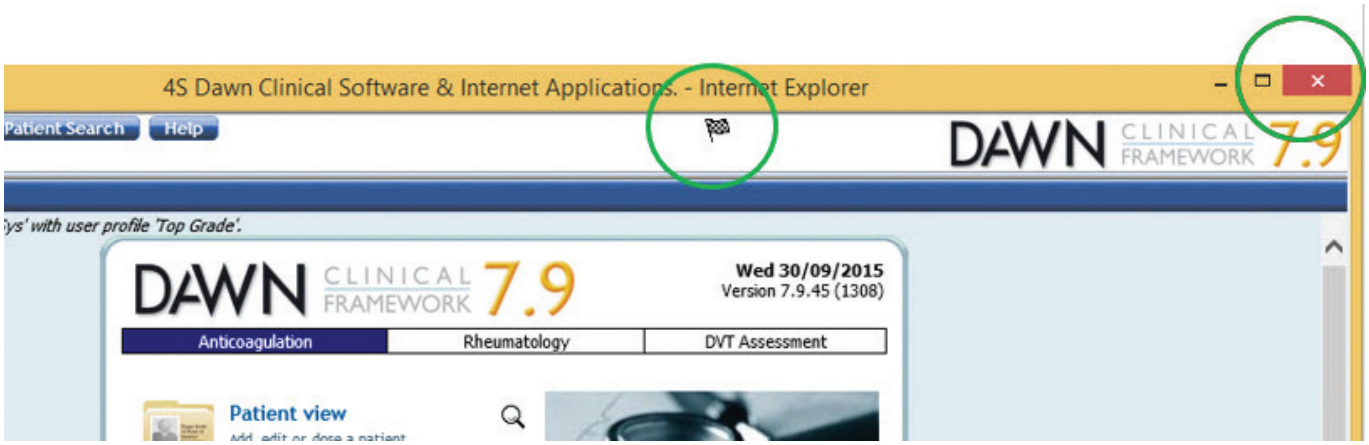
If there are lots of people logged in and using the software, this could potentially affect performance. As a result, we have changed the architecture to make the software 'multi-threaded' so there are now multiple channels of communication between the software program and the database, meaning users actions are responded to faster thereby decreasing queuing time and ensuring more consistent performance.



DAWN AC load balancing is available for customers whose DAWN AC system sits on a Windows 2008 server or higher.

Auto Logout

Customers sometimes receive a message when logging into DAWN telling them that they have reached their maximum user limit even when they know this is not the case. This was caused by users clicking on the 'x' at the top right of the screen rather than the chequered log-out flag (see below).



Clicking on the 'x' does not log the user out of the DAWN system, rather it leaves them logged in until there has been a set period of inactivity from the user, at which point they are automatically logged out. If the user logs back into DAWN before this period of inactivity ends, they are effectively using two user licenses.

This issue has been addressed by making the 'x' the equivalent of the flag so that if either of them is selected, they both immediately terminate the user's DAWN session, freeing up the user license.

Trouble Free Diary Extension

Occasionally when users first login to DAWN AC in the morning, the wait to login can be lengthy and the system slow. This is related to the way DAWN AC manages the clinic diaries and the first person to login sets off the housekeeping task of extending the diaries, which causes this prolonged login and potential missing slots in the diary if the task doesn't complete in time.

The system has now been changed so that the diaries are extended as a scheduled task that runs overnight as a background process so that it doesn't impact users.

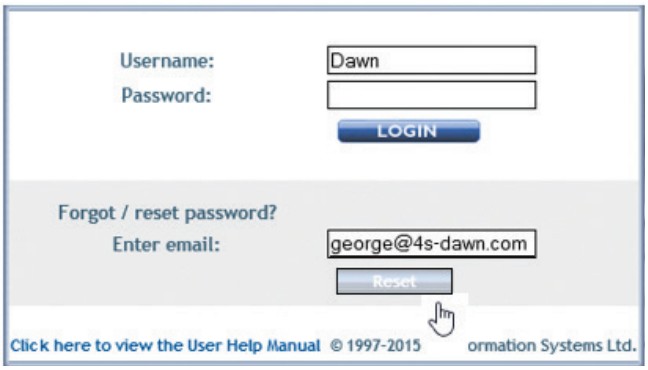
Reset Password Improvements

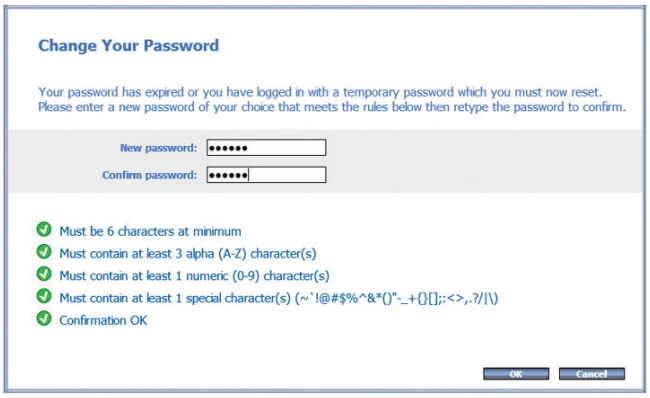
Typically if a user needed a password reset they would need to find a user with administrative rights to reset it for

them, or alternatively contact the 4S DAWN support team. Due to the large number of calls received by the support team for password resets, the system has been improved to make this easier for the user to do themselves.

Users now simply need to enter their email address in the box shown to the right and a temporary password will be emailed to them.

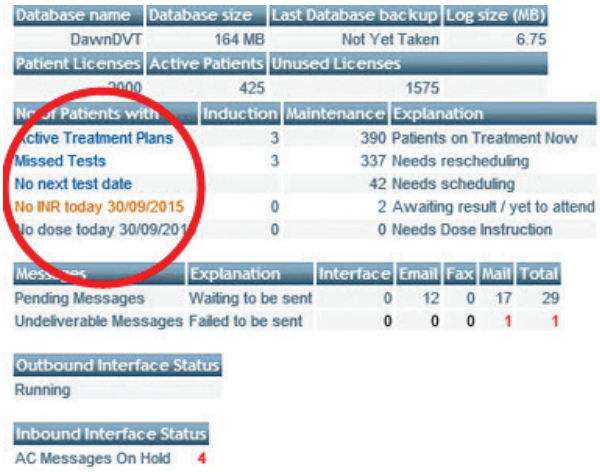
The user would then login with this temporary password and be directed to a screen where they would setup their own password for future logins (see below).





Password reset updates are available in DAWN Version 7.9.44 and above.

Front Screen Tally Hyperlinks



Front screen tallies are a useful tool that enables you to see at a glance the current state of the system, for example how many patients fall into various categories that you need to be aware of such as patients due to attend, patients who failed to attend etc. All the main subsets of patients that you need to focus on are clearly visible.

To enable users to access the patients quickly and easily, we have improved the front screen tallies to incorporate hyperlinks (see image on left). Selecting a hyperlink will jump straight to the relevant list view and have the filter criteria pre-set.

Front screen tally hyperlinks are available in Version 7.9.44 and above.

Timed Messages

While patient reminders have always been available in DAWN, these have had to be manually triggered from either the patient record or the list view. Functionality has now been added to the DAWN system that allows reminders to be sent automatically. For example, if users want to send a reminder to patients who are due for an INR appointment the following day, the system now supports this and enables the user to select the group of patients or HCPs to receive the message, the message method i.e. SMS/text, email, and also the days of the week and the time the messages are supposed to be sent.

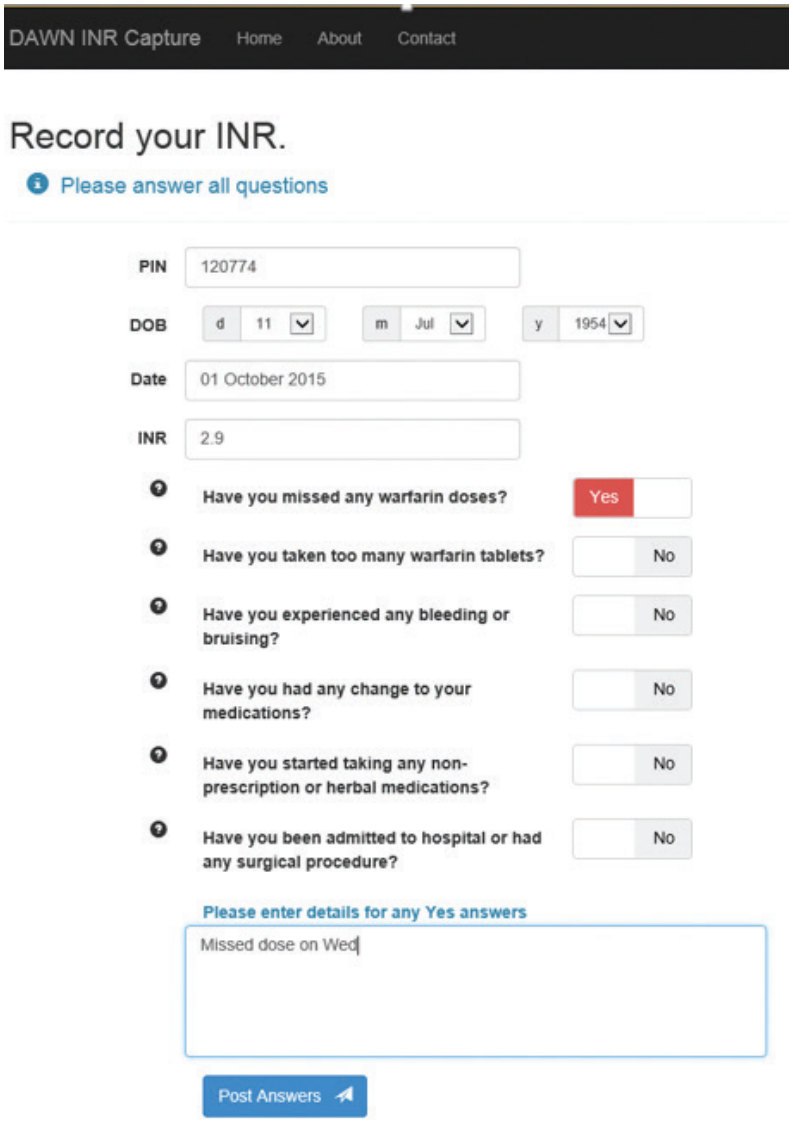
New Communication Tools

DAWN has introduced functionality that supports SMS/text messaging to patients. This can be used for a range of communication to the patient, particularly reminders, and is completed via a third party supplier who fulfils the delivery of the text message.

Emailing PDFs as attachments has also been introduced in DAWN to ensure the consistency and presentation of information to patients, particularly dosing instructions. The presentation and formatting of information can range widely between email clients and various devices used to read emails, potentially resulting in inconsistencies in layout and hard to read information, again particularly for patients who wish to be emailed their dose instructions. A pdf document emailed as an attachment provides a solution to this.

DAWN INR Capture

This new module for DAWN AC facilitates the collection of INR results from domiciliary visits, patient self-testers or remote phlebotomy services.



DAWN INR Capture is an external webpage that sits outside of the hospital firewall and is accessed by the patient or healthcare professional to add the INR, answer the standard set of questions (see image to right) and then submit the form electronically that will then enter the DAWN AC system and populate the patient record accordingly.

Step 1: Patient or HCP is issued a PIN number that is generated by and recorded in DAWN AC. This is issued via SMS, email or letter.

Step 2: Patient or HCP completes the DAWN INR Capture form and submits it (posts answers) electronically.

Step 3: DAWN INR Capture sends the results to DAWN AC via a standard INR interface and populates the patient record accordingly.

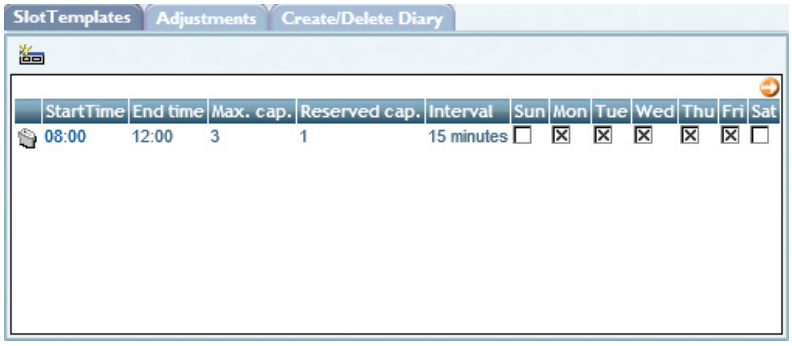
Step 4: HCP authorises the result in DAWN AC and communicates the dosing instruction to the patient as per their standard protocol.

DAWN AC future product developments

Aaron Cosgrove, 4S DAWN Clinical Software

Dynamic Diary

With the dynamic diary feature, users are now able to make changes to diary slots such as max. Cap numbers and start/end times without having to set up a new clinic or delete a diary extension.



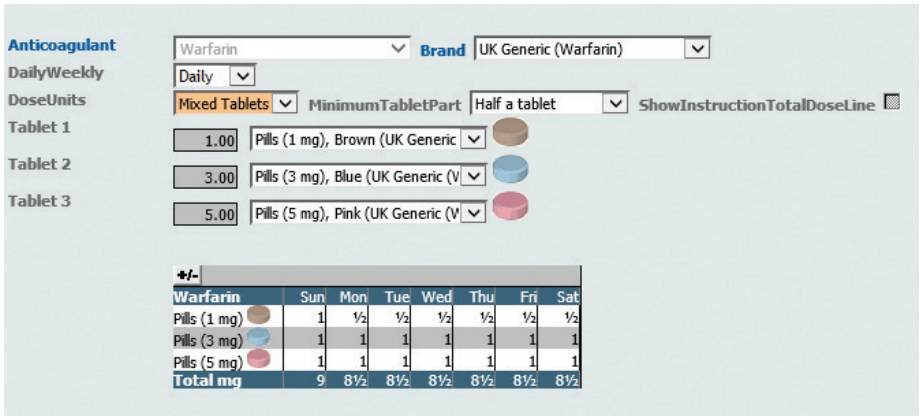
For clinics that have already been extended as per the defined criteria shown in the screenshot above, the slot templates can now be changed within that clinic and these changes will take effect immediately.

The dynamic diary feature also allows you to create adjustments and apply these adjustments to all clinics if required rather than having to manually make the changes to multiple clinics.

Dynamic Dosing

Pre-defined dosing regimes can often be restricting, firstly fitting a patient into an existing set regime and secondly as a change to dosing requires a new regime and instructions to be set up.

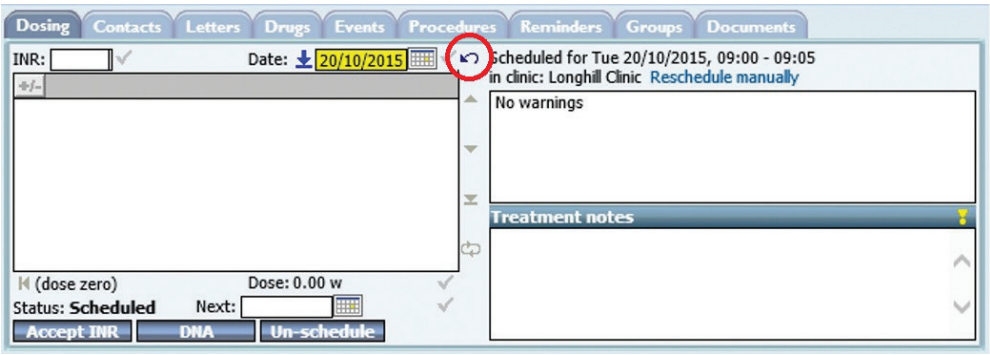
Dynamic dosing screen which will sit in the patient's treatment plan



In order to make dosing easier, 4S DAWN is introducing dynamic dosing which provides flexibility and means that within the patient's treatment plan, dosing/tablet options can be personalised to the individual patient. This also enables changes to be made to the patient's dosing options easily, with changes taking effect immediately rather than having to set up a new dosing regime. An algorithm has been developed that will automatically generate instructions based on the selection made.

Easy 'Accept Dosing' Undo

If an INR result and dose has been accepted and for whatever reason you need to undo the dose, previously you would need to go through a number of steps that would ultimately remove the INR and the dose. This process will now be replaced with a simple 'Undo' arrow in the dosing box which, with a single click, will return you to the previous state without having to go through numerous steps first.



Dosing panel shows 'Undo' arrow

NOAC/DOAC Module Updates

Serum Creatinine Units

You can now choose whether to record serum creatinine units in µmol/L or mg/dL (previously µmol/L was the only option). You can set your preferred option within the system settings.

Additional Therapeutic Indications

Dabigatran:
DVT - Provoked
DVT - Unprovoked
PE - Provoked
PE - Unprovoked
Recurrent DVT
Recurrent PE

Rivaroxaban:
Total Hip Replacement Surgery
Total Knee Replacement Surgery

Additional Permitted Regimes

Dabigatran:
Dabigatran 75mg Once Daily (recommended for total knee or hip replacement patients with moderate renal impairment and concurrent treatment with verapamil or at significant risk of bleeding).

Rivaroxaban:
Rivaroxaban 10mg Once Daily (normal dose for total knee or hip replacement patients)

Using the Variability of INRs to Indicate the Risk of an Event in DAWN AC – Variance Growth Rate (VGR)

Syd Stewart, Managing Director, 4S DAWN Clinical Software

It is widely agreed that neither the INR alone nor the % Time in Therapeutic Range (TTR) are dependable predictors of clinical events in patients receiving oral anticoagulation.

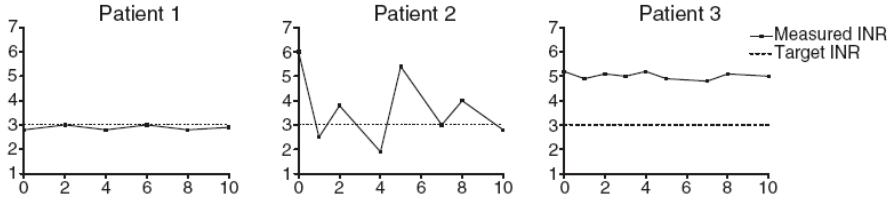
A new study, *'The clinical evaluation of International Normalised Ratio variability and control in conventional oral anticoagulant administration by use of the variance growth rate'* published by Poller, L., Ibrahim, S. and Jespersen, J. in the Journal of Thrombosis and Haemostasis looked at the possible value of an additional calculation (the variance growth rate (VGR)) as an addition to %TTR in predicting clinical events.

This study took data from a previous prospective multicentre randomised trial comparing DAWN AC computer aided treatment with experienced medical staff *(Poller L, et al. Multicentre randomised study of computerised anticoagulant dosage. Lancet. 1998, 352: 1505-09)*. In total, 661 control patients were matched to 158 event

cases (bleeding, thromboembolism or death). The VGR and %TTR were measured over three time periods, overall follow-up; 6 months; and 3 months before an event.

The VGR measurements look at the variability between the patient's INR values to determine how 'stable' they are. Three methods for calculating the VGR were assessed within the study and the following figures graphically illustrate the three methods.

Method A measures the degree to which a patient's INR differs from their target INR over a prolonged period, whilst Method B1 measures the degree to which a patient's current INR differs from the previous one. Method B2 is a similar measure to Method B1 but with some minor differences to the denominator value, however, neither Method B1 nor B2 take into account how close the patient is to their target INR.



Method A = 0.01
Method B1 = 0.01
Method B2 = 0.01

Method A = 1.04
Method B1 = 4.06
Method B2 = 4.64

Method A = 3.23
Method B1 = 0.03
Method B2 = 0.03

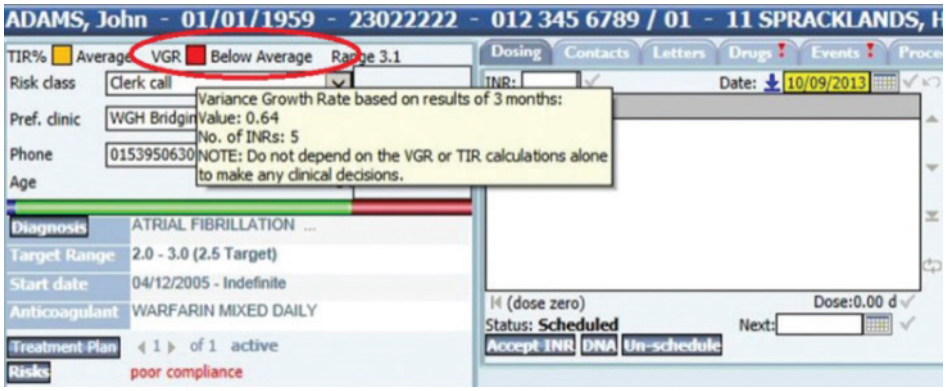
Key Findings:

- %TTR is a reasonable predictor of clinical events only when calculated over the last three or six months of treatment
- %TTR showed no correlation with bleeding events when calculated over any period of treatment
- %TTR may be a predictor of thrombotic events when calculated over the last six months of treatment
- The Variance Growth Rate (VGR-A) showed a very strong correlation with clinical events when calculated over the last three or six months of treatment
- The Variance Growth Rate (VGR-A) showed a good correlation with bleeding events when calculated over the last three or six months of treatment
- The Variance Growth Rate (VGR-B1) showed a very strong correlation of bleeding events when calculated over the last three months of treatment
- The Variance Growth Rate (VGR-A) may be a reasonable predictor of thrombotic events when calculated over the last three months of treatment

It should be noted that there were very few thrombotic events, which made the prediction of events difficult to measure.

In conclusion, the study determined that INR monitoring with a measure such as the VGR and %TTR, three to six months before the current INR, may offer additional safety by detecting and isolating patients who may be at increased risk of possible adverse episodes.

It should be noted that a large prospective trial is needed to confirm the findings above.



As a result of the findings of the study, the 4S DAWN team have developed the VGR calculation within DAWN AC as illustrated.

This is now available to customers and is offered as an option, with users having the choice as to whether the VGR is displayed on the patient records.

For more information on DAWN AC Products and Services:
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Or Internationally 44 15395 63091. Fax 44 15395 62475

E-mail: sales@4s-dawn.com
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