Optimizing the Management of Warfarin Therapy

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New York
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How could this patient have been managed better . . .

A 71 year old male was started on warfarin for an embolic CVA related to atrial fibrillation. He was discharged after being switched from heparin to warfarin with an INR of 2.1 on the day of discharge. An INR 4 days later was 2.8. His next INR was ordered for 3 weeks later; he obtained the INR in the morning and went home waiting for the call. Later that day, at home, he was found comatose. The INR pending from the morning was 14.6. The patient was found to have a massive intracranial hemorrhage and he subsequently died.

Even without knowing more information about this case, what went wrong? There are at least 2 management deficits, both of which could have been avoided.

The Dilemma of Current Oral Anticoagulant Therapy

- Warfarin has a narrow therapeutic window of effectiveness and safety
- Many factors influence a patient's ability to stay in that window (diet, meds, illnesses)
- Frequent monitoring is required to maintain patients in the therapeutic window
- Monitoring is labor intensive, complex and may lead to under use of therapy
- Warfarin has a high rate of adverse events in real world and may lead to under use of therapy

Anticoagulation Therapy
Impediments to Care

Patient Related

- Travel to office, lab
- Wait to be seen
- Venipunctures
- Reports delayed
- Costs

Physician Related

- Scheduling tests
- Reports delayed
- Contacting Patient
- Reimbursement

Technology Related

- Sample handling
- Availability of result
- Accuracy, consistency

Goals of Warfarin Therapy

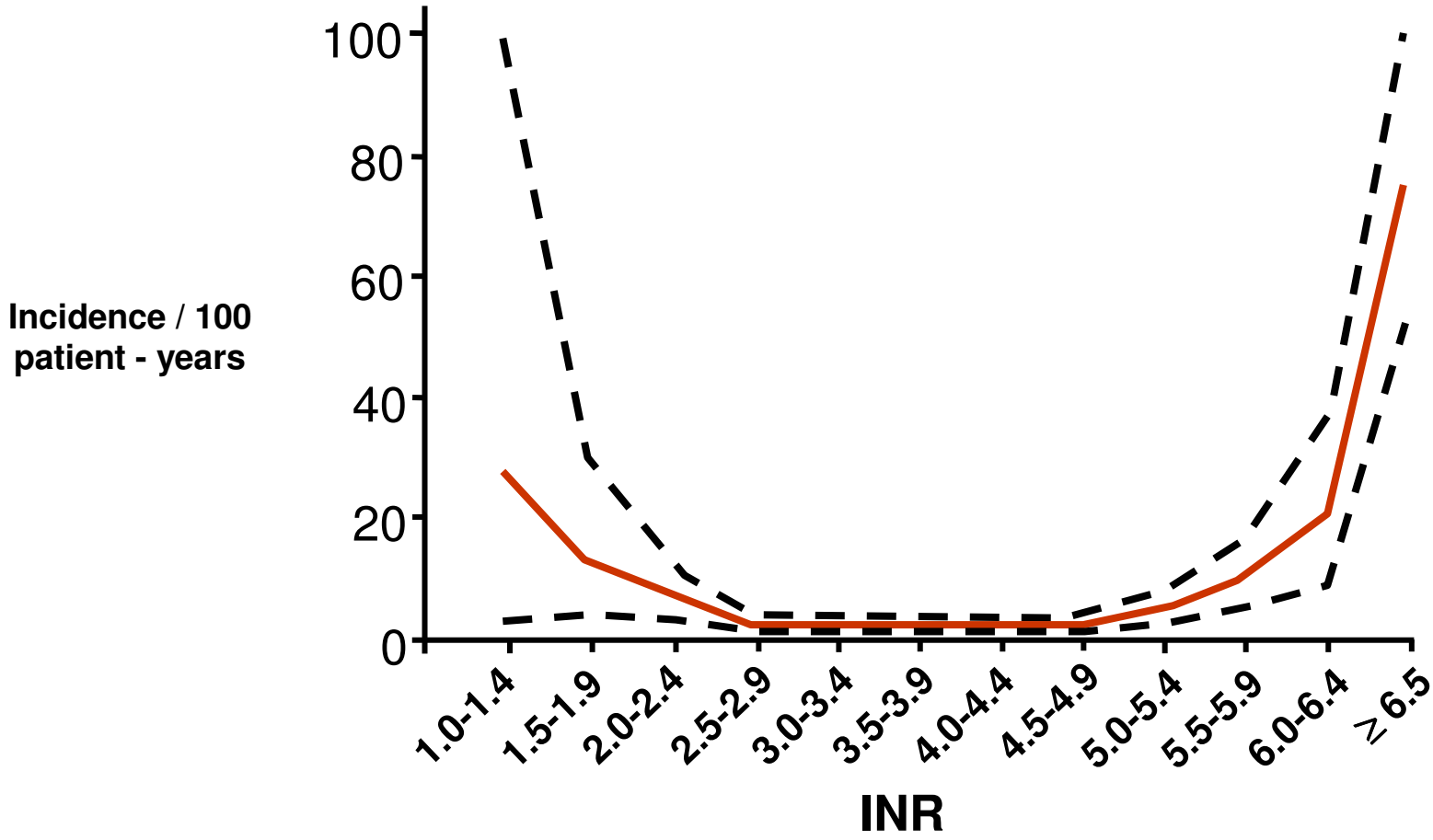
To achieve the greatest reduction in thromboembolism with the lowest incidence of bleeding.

This involves knowing:

- When to use
  (proper indications)
- How much to use
  (proper therapeutic range)
- How to use
  (proper dose management)

Warfarin Has a Narrow Therapeutic Window

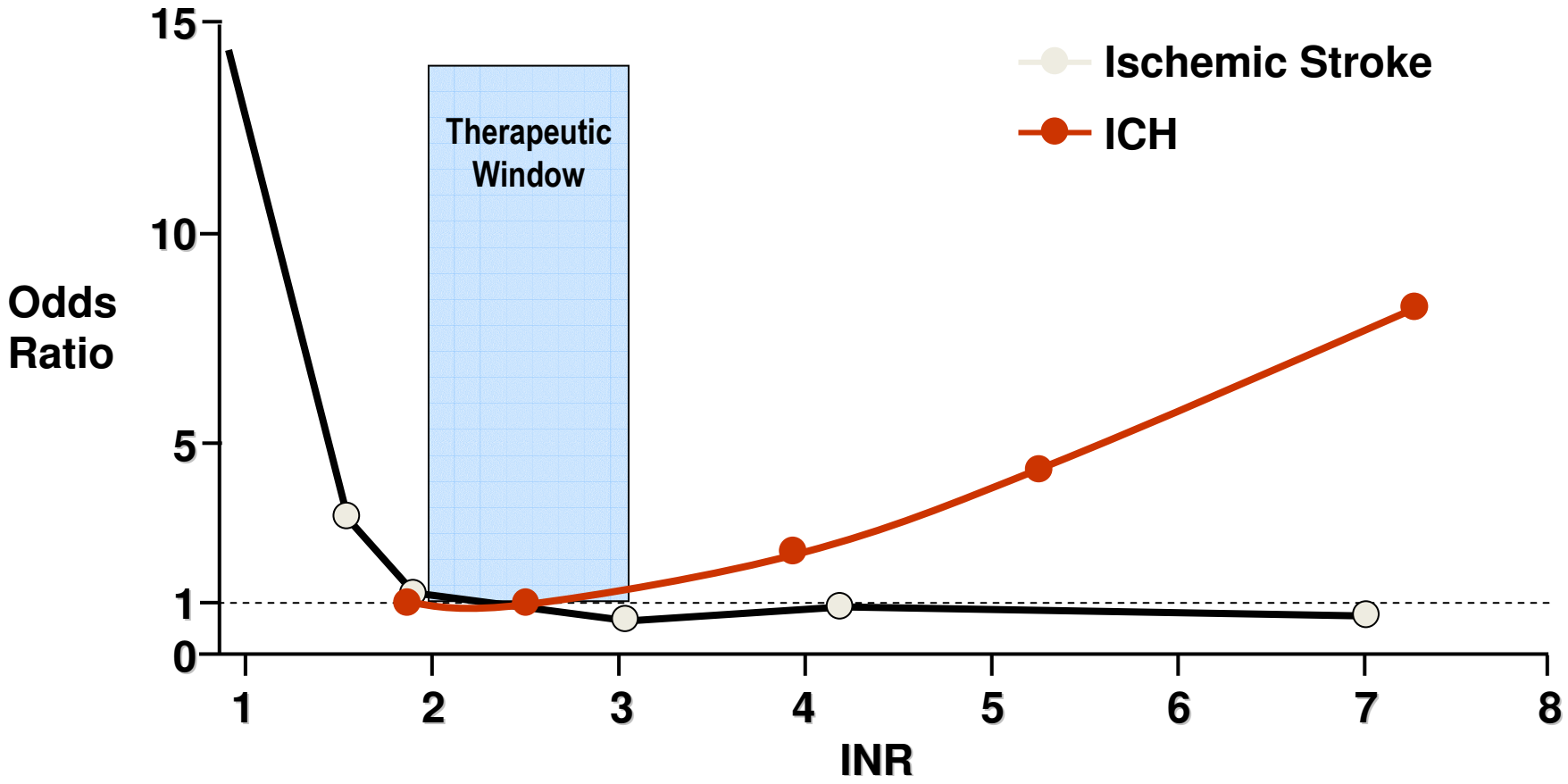
Relationship Between Clinical Events and INR Intensity in Patients with Prosthetic Valves



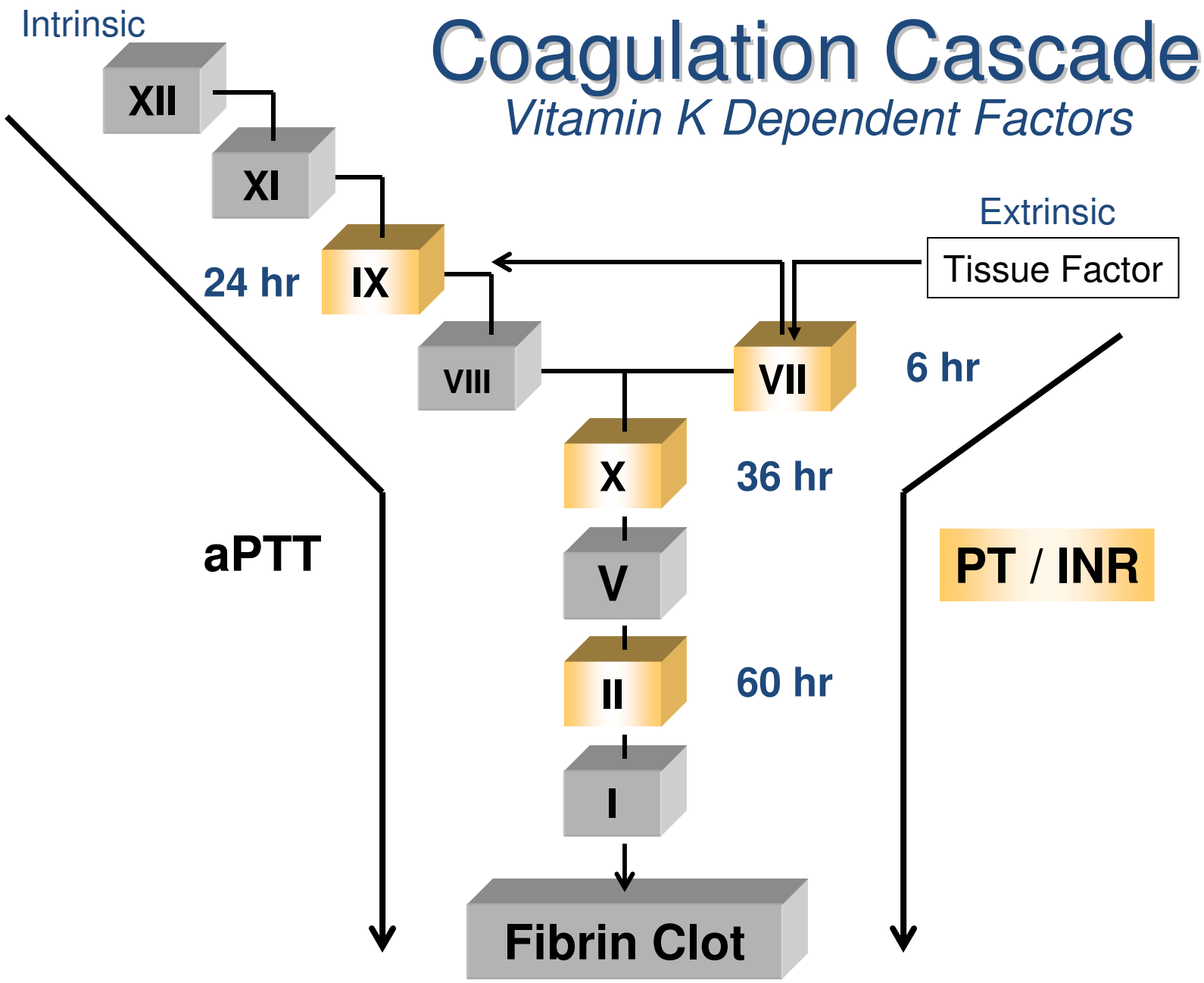
Cannegeiter et al

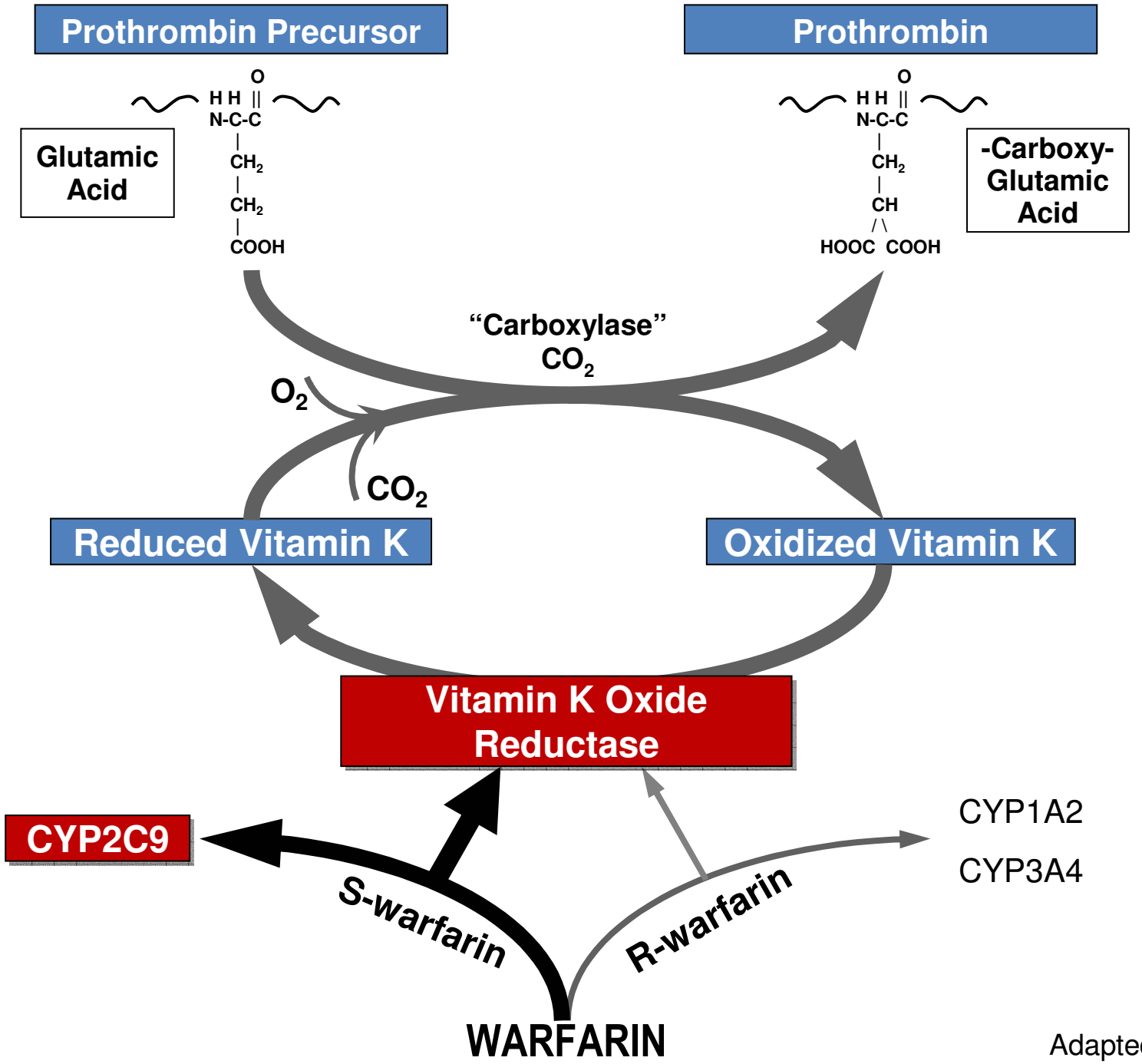
Warfarin Has a Narrow Therapeutic Window

Relationship Between Clinical Events and INR Intensity in Patients with Atrial Fibrillation



1. Hylek EM et al. *Ann Intern Med.* 1994;120:897.
2. Hylek EM et al. *N Engl J Med.* 1996;335:540.


Coagulation Cascade
Vitamin K Dependent Factors
Intrinsic
XII
XI
IX
24 hr
VIII
Extrinsic
Tissue Factor
VII
6 hr
X
36 hr
V
II
60 hr
I
Fibrin Clot
aPTT
PT / INR



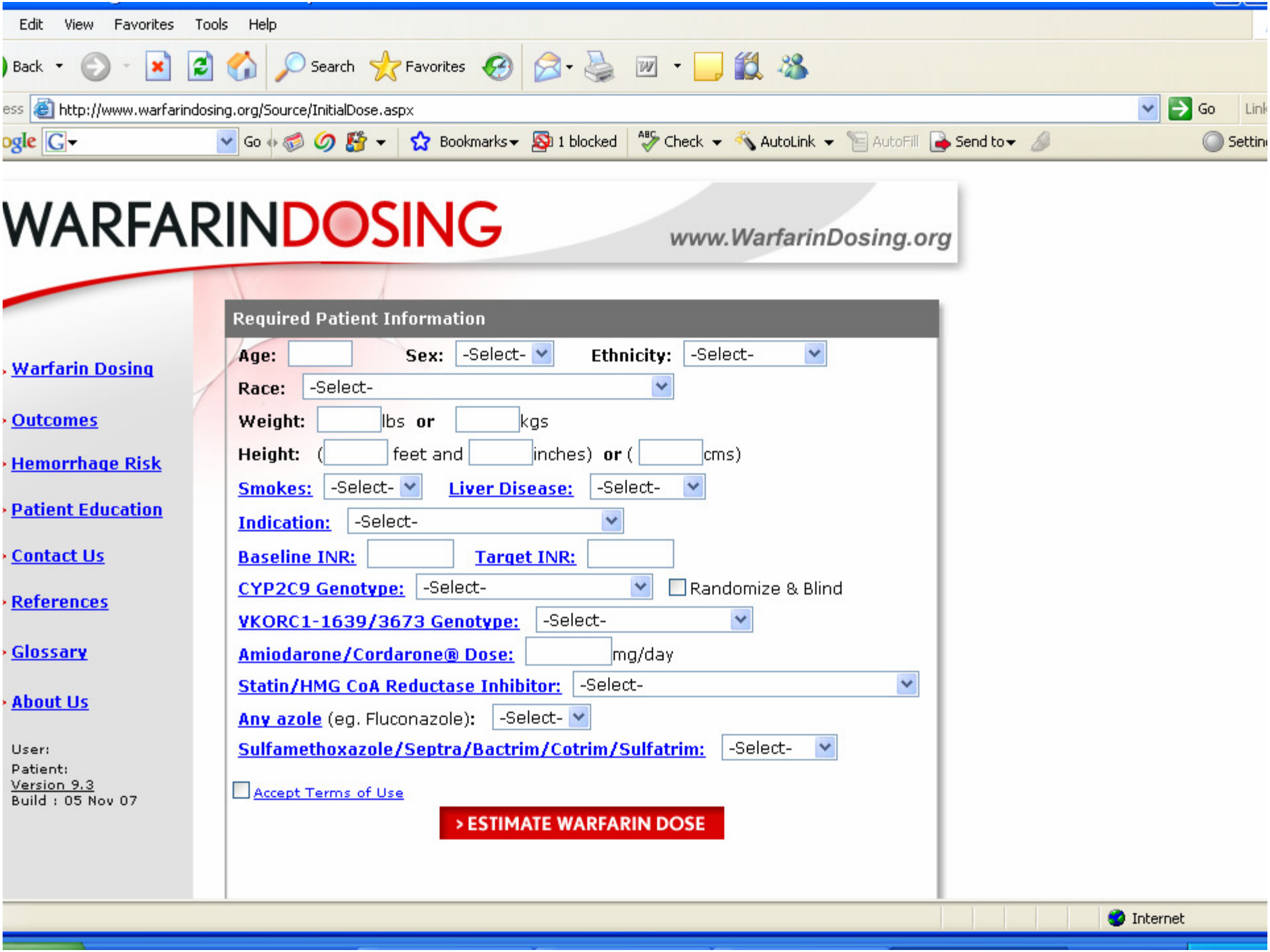
Adapted, B. Gage

Warfarin dosing equation

Exp[0.9751-0.3238 x VKOR3673G>A + 0.4317 x BSA – 0.4008 x CYP2C9*3 – 0.00745 x Age – 0.2066 x CYP2C9*2 + 0.2029 x Target INR – 0.2538 x Amiodarone + 0.0922 x Smokes – 0.0901 x African American race + 0.0664 x DVT/PE]

The SNPs are coded 0 if absent, 1 if heterozygous, and 2 if homozygous and race is codes as 1 if African American and 0 otherwise

B. Gage. www.warfarindosing.org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Outcomes
Hemorrhage Risk
Patient Education
Contact Us
References
Glossary
About Us
User:
Patient:
Version 9.3
Build : 05 Nov 07
Required Patient Information
Age: Sex: -Select- Ethnicity: -Select-
Race: -Select-
Weight: lbs or kgs
Height: (feet and inches) or (cms)
Smokes: -Select- Liver Disease: -Select-
Indication: -Select-
Baseline INR: Target INR:
CYP2C9 Genotype: -Select- Randomize & Blind
VKORC1-1639/3673 Genotype: -Select-
Amiodarone/Cordarone® Dose: mg/day
Statin/HMG CoA Reductase Inhibitor: -Select-
Any azole (eg. Fluconazole): -Select-
Sulfamethoxazole/Septra/Bactrim/Cotrim/Sulfatrim: -Select-
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Models of AC Management

- Routine medical care or usual care (UC)
- Anticoagulation clinic care (ACC)
- Point-of-care (POC) testing
  - Provider testing and dosing
  - Patient self-testing (PST), but
    - Dosing by provider
  - Patient self-management (PSM), with
    - Dosing by patient

1. Campbell PM et al. *Dis Manag Clin Outcomes.* 2000;2:1-8. 2. Ansell JE. In: Ansell JE, Oertel LB, Wittkowsky AK, eds. *Managing Oral Anticoagulation Therapy*. 2nd ed. St. Louis, Mo: Facts and Comparisons; 2003;44:1-6.

The essential elements of an anticoagulation management service

Active rather than passive dose management.

Dedicated personnel to proactively schedule, confirm, and track appointments and INR results and to maintain patient communication.

Dose manager with appropriate training or experience

Physician, nurse practitioner, physician assistant, or pharmacist
In the small physician office, this is usually the responsibility of the physician.

Documentation of all dosing decisions and patient interactions

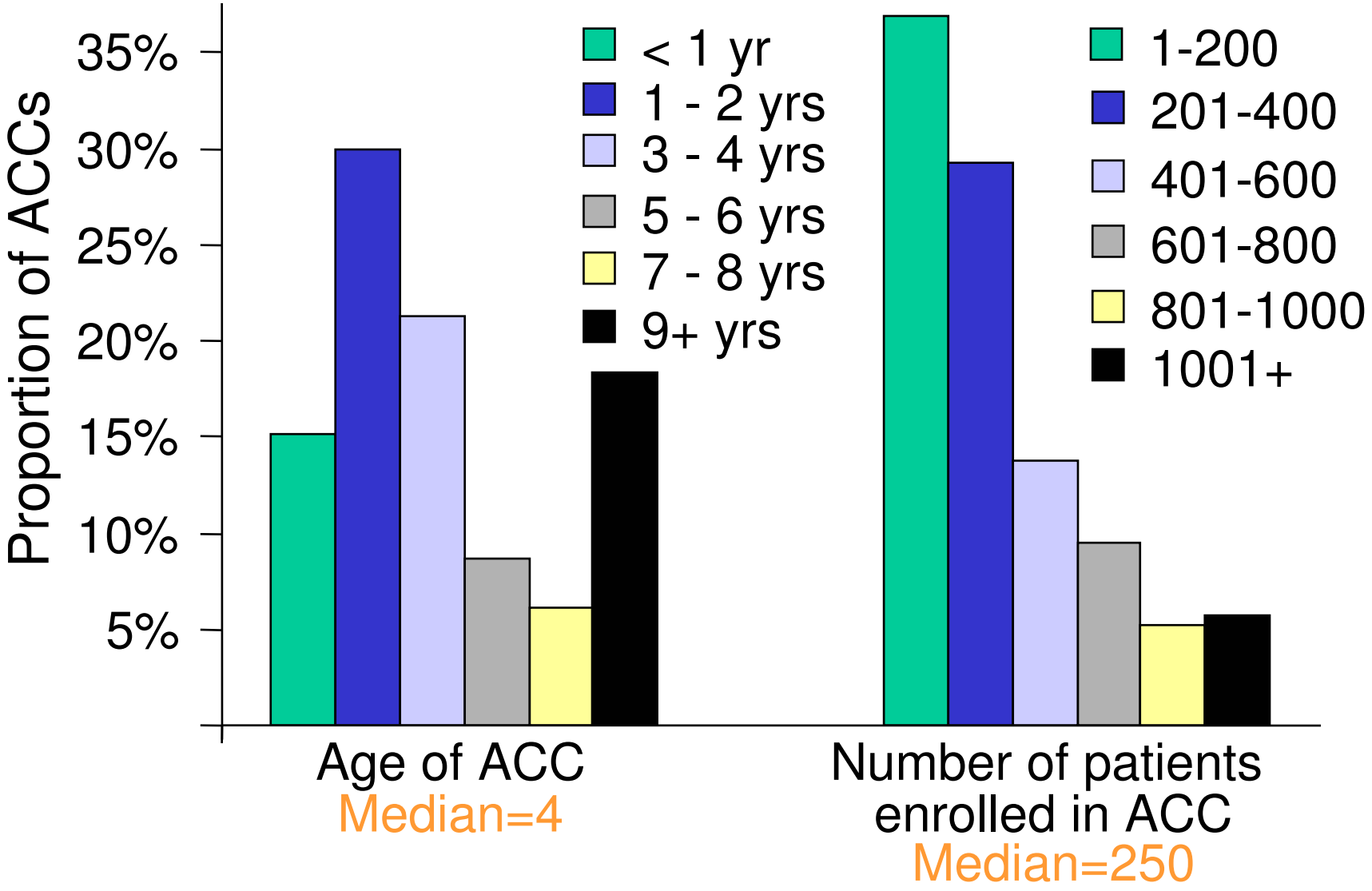
Document each encounter (paper or electronically):current dose, INR, new dose, next appointment and any anticoagulation-related problems.
Flow sheets to track current and previous INRs is essential.

Policies or guidelines to facilitate systematic care

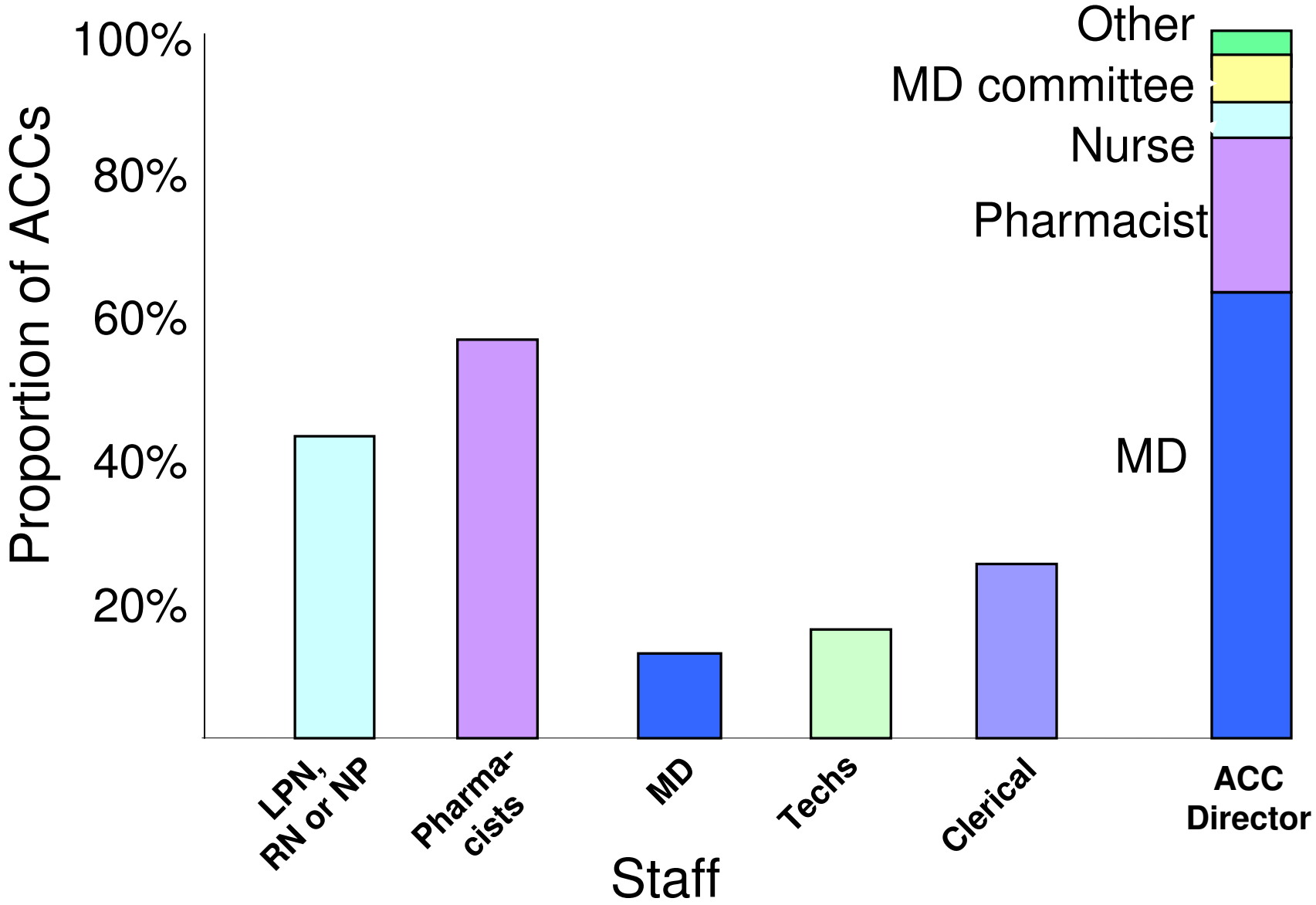
Policies should include guidelines for:
AC indications; target INR and range; basic elements of patient education; initiation and maintenance dosing policy; frequency of monitoring; management of non-therapeutic INRs; management of bleeding; use of vitamin K; management of AC during invasive procedures; duration of anticoagulation; INR management responsibility when physician not available (coverage)

Age & Size of ACCs

(N=233)

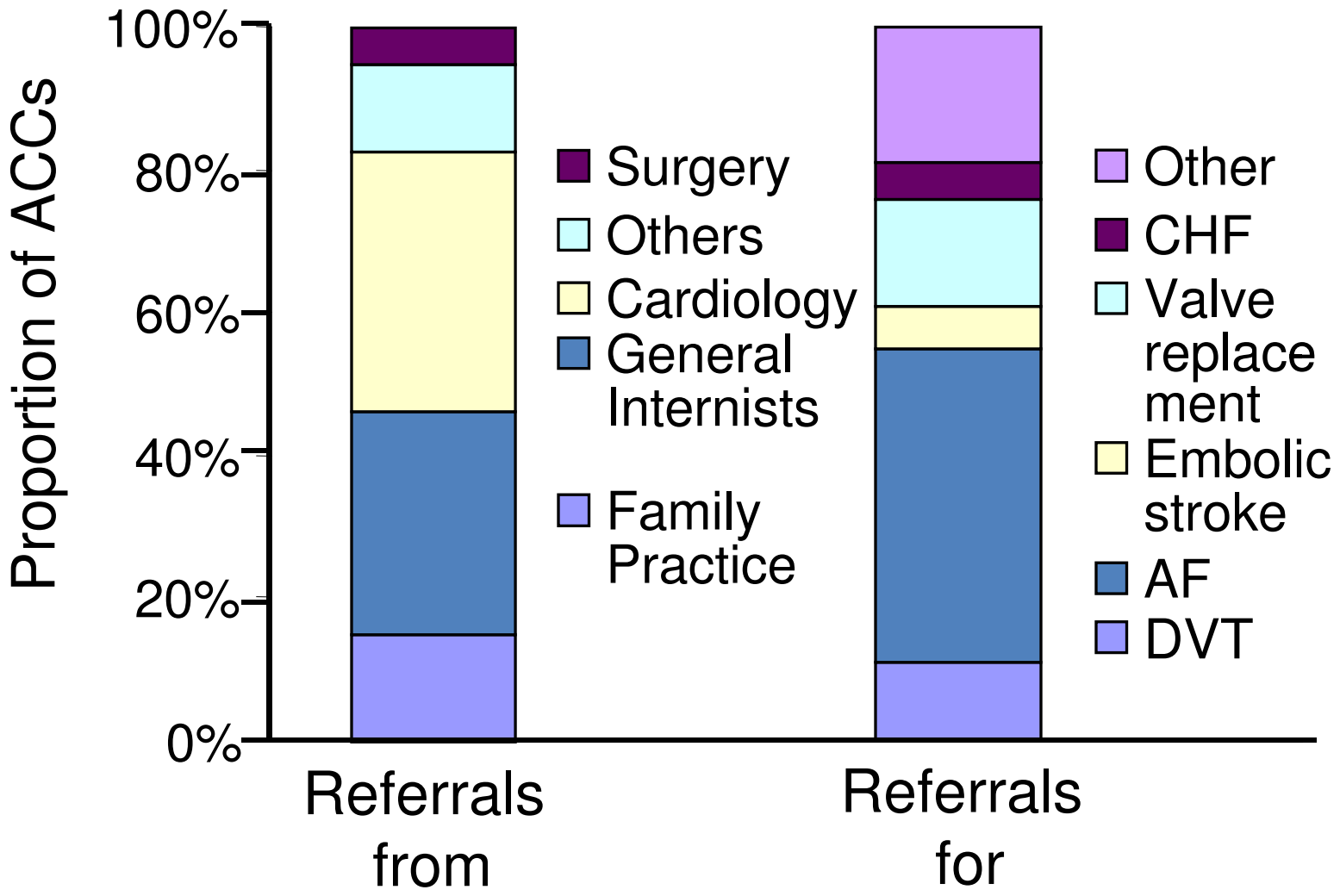


ACC Staffing*

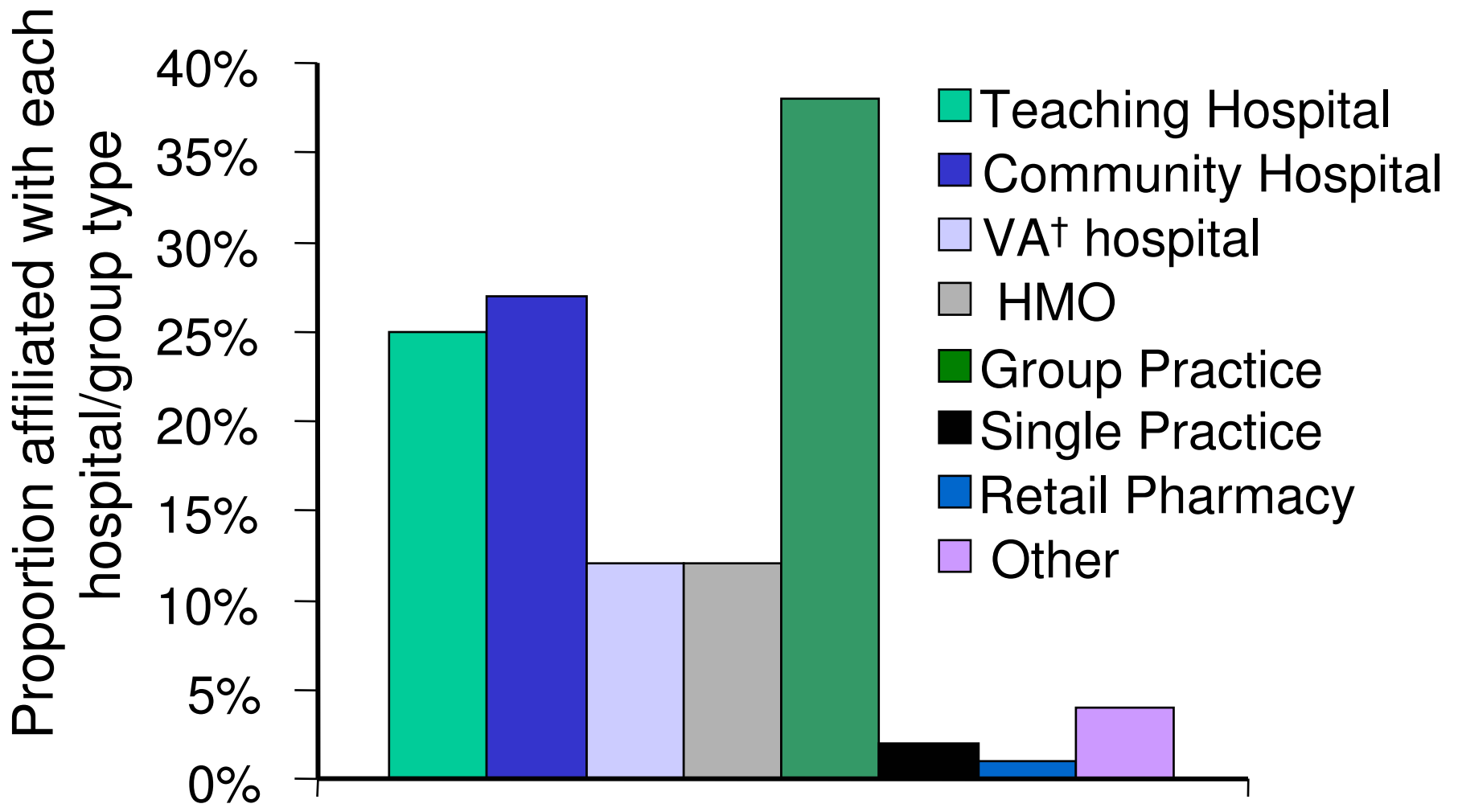


* Multiple staff types possible

Type of Referrals Received by ACCs



ACC Affiliation*



** Multiple affiliations possible.* *† Veteran's Administration*

TTR vs Model of AC Management

Study	Model of Care	TTR	Above Range	Below Range
Garabedian 1985	UC	64	-	-
Gottlieb 1994	UC	50	30	20
Beyth 1997	UC	33	16	51
Horstkotte 1998	UC	59	-	-
Sawicki 1999	UC	34	16	50
Holm 1999	UC	63	8	29
Garabedian 1985	ACC	86	-	-
Conte 1986	ACC	59	12	29
Lundstrom 1989	ACC	92	-	-
White 1989	ACC	75	-	-
Seabrook 1990	ACC	86	7	7
Cannegeiter 1995	ACC	61	8	31
Ansell 1995	ACC	68	10	22
Palaretti 1996	ACC	68	6	26

Range 33-64% Mean 50.5%

Range 59-92% Mean 74.4%

Author Year	Type of Patient	Indi-cation	Interven-tion	# Patient	# Pt-Yrs	Major Bleed (%)	Rec TE (%)
UC: Retrospective Trials							
Gitter 1995	non incept cohort	Mixed	UC	261	221	8.1	8.1
Beyth 1998	inception cohort	Mixed	UC	264	440	5.0	NA
Steffensen 1997	inception cohort	Mixed	UC	682	756	6.0	NA
Willey 2004	inception cohort	VTE	UC	2,090	1,441	2.8	6.2
Total				**3,297**	**2,858**	**4.4**	**6.4**
AMS: Retrospective Trials							
van der Meer 1993	non incept cohort	Mixed	AMS	6,814	6,085	3.3	NA
Cannegeiter 1995	non incept cohort	MHV	AMS	1,608	6,475	2.5	0.7
Veeger 2005	inception cohort	VTE	AMS	2,304	1,441	2.8	6.3
Total				**10,726**	**14,001**	**2.9**	**1.7**
AMS: Prospective							
Palareti 1996	inception cohort	Mixed	AMS	2,745	2,011	1.4	3.5
Abdehafiz 2004	inception cohort	AF	AMS	402	636	1.7	1.5
Total				**3,147**	**2,647**	**1.5**	**3.0**

Ansell et al. Chest 2008;133:160S

Author Year	Type of Patient	Indi-cation	Interven-tion	# Patient	# Pt-Yrs	Major Bleed (%)	Rec TE (%)
UC vs AMS: Retrospective Trials							
Cortelazzo 1993	NA	MHV	**UC**	271	677	**4.7**	**6.6**
	NA	MHV	**AMS**	271	669	**1** p<0.01 0.21(0.09,0.52)	**0.6** p<0.01 0.09(0.03,0.29)
Chiquette 1998	NA	Mixed	**UC**	142	102	**3.9**	**11.8**
	NA	Mixed	**AMS**	82	199	**1.6** p<0.5; 0.41(0.08,2.22)	**3.3** p<0.05; 0.28(0.08,0.99)
Witt 2005	NA	Mixed	**UC**	3,322	1,661	**2.2**	**3.0**
	NA	Mixed	**AMS**	3,323	1,661	**2.1** p=NS; 0.95(0.57,1.60)	**1.2** p<0.05; 0.40(0.22,0.71)
UC vs AMS: Randomized Trials							
Matchar 2002[52]	inception cohort	AF	**UC**	190	NA	**1.6**	**7.4**
	inception cohort	AF	**AMS**	173	NA	**1.7** 1.10(0.22,5.37)	**5.2** 0.71(0.31,1.59)
Wilson 2003[53]	inception cohort	Mixed	**UC**	106	109	**0.9**	**1.8**
	inception cohort	Mixed	**AMS**	112	112	**1.8** 1.95(0.18,21.16)	**0.9** 0.63(0.44,0.92)

AC Clinics in Other Countries

Country	Pop x 10^6	On OAC x 10^3	In ACC	TTR 2-3	Test Interval
Canada	32	275	5 %	62.8	24.3
England	63	750	80 %	NA	NA
France	60	600	0 %	59.3	23.6
Italy	60	650	25 %	69.5	20.0
Neth'lands	6.3	325	100 %	NA	NA
Spain	42	400	90 %	64.9	30.8
US	280	2500	25 %	58.1	25.3

Pengo. ISAM Study

Keys to Developing an Organized Model of Anticoagulation Management

- Involving key players
- Institutional commitment
- Business plan
- Policies and procedures
- Education / certification of providers

Developing an ACC: Staffing[1]

Panel Size	Predicted INRs/Day	Hrs/Day	% FTE
100	10	2	0.25
200	20	4	0.50
300	30	6	0.750
400	40	8	1.0

[1]Dose management only

From L Oertel 1998

Technology Advances:
Offers a new paradigm for monitoring

- Use of capillary whole blood[1,2]
  - Allows fingerstick sampling[2]
  - Appropriate for self-testing[1]
- Consistency of INR results[1]
- Portability[1]
  - Can be done anywhere
- Simplicity[1]
  - Patient can easily perform test

1. Leaning KE, Ansell JE. *J Thromb Thrombolysis*. 1996;3:377-383. 2. Ansell JE. In: Ansell JE, Oertel LB, Wittkowsky AK, eds. *Managing Oral Anticoagulation Therapy*. 2nd ed. St. Louis, Mo: Facts and Comparisons; 2003;44:1-6.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HEMOCHRON®
Signature Elite™
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CHARGE
START
ABC / 123
NOTE
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DATA BASE
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SPACE
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MNO
4
5
6
PQRS
TUV
WXYZ
7
8
9
CANCEL
0
MENU
ENTER


INRatio
INR=2.4
OK
HemoSense

Time in Therapeutic Range

PSM vs UC or ACC

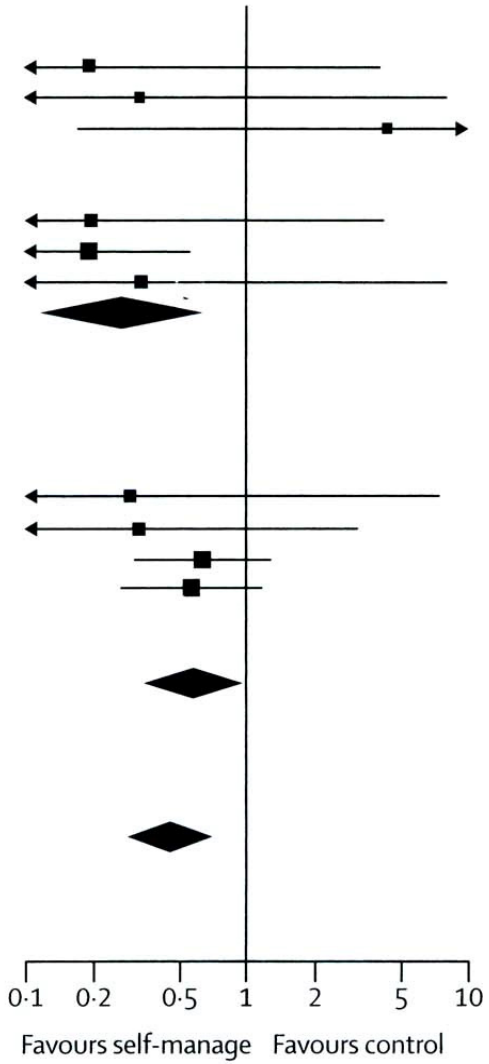
Study	Comparators	TTR	Hem & TE
Horstkotte 1996 (RCT)	PSM vs UC	**92 % vs 59 %**	5.4% vs 14.5%
Hasenkam 1997 (RCT)	PSM vs UC	**77 % vs 53 %**	no AEs
Sawicki 1999 (RCT)	PSM vs UC	**57 % vs 34 %**	4.4% vs 6.7%
Koertke 2001 (RCT)	PSM vs UC	**78 % vs 61 %**	2.9% vs 4.7%
Preiss 2001 (cohort)	PSM vs UC	**74 % vs 63 %**	3.3% vs 4.7%
Ansell 1995 (case control)	PSM vs ACC	**88 % vs 68 %**	no AEs
Watzke 2000 (RCT)	PSM vs ACC	**86 % vs 80 %**	4% vs 0
Cromheecke 2000 (cross-over)	PSM vs ACC	**55 % vs 49 %**	no AEs
Gadisseur 2003 (RCT)	PSM vs ACC	**71 % vs 68 %**	NA
Menendez 2005 (IRCT)	PSM vs ACC	**59 % vs 56 %**	1.6% vs 4.1%

Mean 75% VS 54%

Mean 72% VS 64%

Thromboembolism with PST or PSM

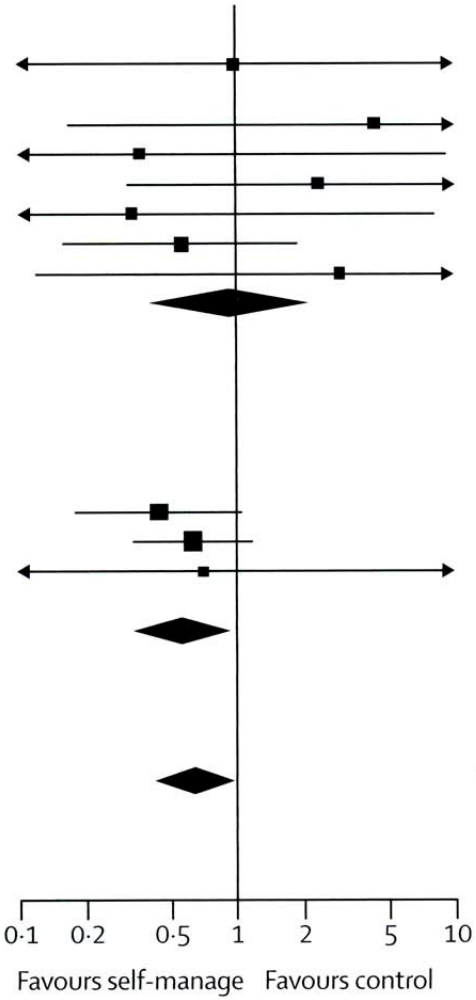
Study or sub-category	Self-management n/N	Control n/N	OR (fixed) 95% CI	Weight %	OR (fixed) 95% CI
01 Self-adjust*					
Sawicki 1999	0/83	2/82		3·50	0·19 (0·01–4·08)
Cromheecke 2000	0/49	1/49		2·08	0·33 (0·01–8·22)
Sidhu 2001	1/34	0/48		0·56	4·34 (0·17–109·88)
Fitzmaurice 2002	0/23	0/26			Not estimable
Gadisseur 2003 (a)	0/47	0/110			Not estimable
Sunderji 2004	0/69	2/70		3·45	0·20 (0·01–4·18)
Menendez-Jandula 05	4/368	20/369		27·68	0·19 (0·06–0·57)
Voller 2005	0/101	1/101		2·09	0·33 (0·01–8·20)
Subtotal (95% CI)	774	855		39·37	0·27 (0·12–0·59)
Total event: 5 (self-management), 26 (control)					
02 Non-adjust †					
White 1989	0/26	1/24		2·14	0·30 (0·01–7·61)
Horstkotte 1998	1/75	3/75		4·15	0·32 (0·03–3·19)
Beyth 2000	14/163	21/162		26·98	0·63 (0·31–1·29)
Kortke 2001	12/305	20/295		27·37	0·56 (0·27–1·17)
Gadisseur 2003 (b)	0/52	0/111			Not estimable
Gardiner 2004	0/29	0/24			Not estimable
Subtotal (95% CI)	650	691		60·63	0·57 (0·35–0·93)
Total event: 27 (self-management), 45 (control)					
Total (95% CI) ‡	1424	1546		100·00	0·45 (0·30–0·68)
Total event: 32 (self-management), 71 (control)					



Heneghan et al. Lancet 2006;367:404

Major Hemorrhage with PST and PSM

Study or sub-category	Self-management n/N	Control n/N	OR (fixed) 95% CI	Weight %	OR (fixed) 95% CI
01 Self-adjust*					
Sawicki 1999	1/83	1/82		1·84	0·99 (0·06–16·06)
Cromheecke 2000	0/49	0/49			Not estimable
Sidhu 2001	1/34	0/48		0·74	4·34 (0·17–109·88)
Fitzmaurice 2002	0/23	1/26		2·56	0·36 (0·01–9·32)
Gadisseur 2003 (a)	2/47	2/110		2·12	2·40 (0·33–17·57)
Sunderji 2004	0/69	1/70		2·74	0·33 (0·01–8·32)
Menendez-Jandula 05	4/368	7/369		12·81	0·57 (0·16–1·96)
Voller 2005	1/101	0/101		0·91	3·03 (0·12–75·26)
Subtotal (95% CI)	774	855		23·73	0·93 (0·42–2·05)
Total event: 9 (self-management), 12 (control)					
02 Non-adjust †					
White 1989	0/26	0/24			Not estimable
Beyth 2000	8/163	17/162		30·04	0·44 (0·18–1·05)
Kortke 2001	17/305	25/295		44·46	0·64 (0·34–1·21)
Gadisseur 2003 (b)	0/52	1/111		1·77	0·70 (0·03–17·51)
Gardiner 2004	0/29	0/24			Not estimable
Subtotal (95% CI)	575	616		76·27	0·56 (0·34–0·93)
Total event: 25 (self-management), 43 (control)					
Total (95% CI) ‡	1349	1471		100·00	0·65 (0·42–0·99)
Total event: 34 (self-management), 55 (control)					



Heneghan et al. Lancet 2006;367:404

Benefits of POC

Testing by Provider

- Simplifies anticoagulation management[1]
- Immediate and accurate INR results[2]
- Provider communicates results and dosage adjustments directly to patient[2]
  - May improve patient outcomes
  - Face-to-face instruction may improve quality of care
- Improves business and office efficiency by avoiding[2,3]
  - Venous draw
  - Proper handling of sample
  - Sending to central laboratory for testing

1. Hirsh J et al. *J Am Coll Cardiol.* 2003;41:1633-1652. 2. Cheung DS et al. *Am J Geriatr Cardiol.* 2003;12:283-287. 3. Roche Diagnostics. *CoaguChek System: Why Use?* Available at: http://www.coaguchek-usa.com/information_for_professionals/why_use/sam/content.html. Accessed May 12, 2006.

Benefits of POC
Patient self testing

- Allows more frequent testing
  - Longer TTR may improve patient outcomes
  - Ability to detect INR changes may allow detection prior to clinically significant event
- Enhances patient involvement in own care
- Provides consistency of instrumentation and reagents

Jacobson AK. In: Ansell JE, Oertel LB, Wittkowsky AK, eds. *Managing Oral Anticoagulation Therapy*. 2nd ed. St. Louis, Mo: Facts and Comparisons; 2003;45:1-6.

Barriers to PST/PSM

- Lack of physician awareness or acceptance[1,2]
- Fear it will lead to unintended self-management[3]
- Implementation of PST/PSM[3]
- Reimbursement[3]

1. Jacobson AK. In: Ansell JE, Oertel LB, Wittkowsky AK, eds. *Managing Oral Anticoagulation Therapy*. 2nd ed. St. Louis, Mo: Facts and Comparisons; 2003;45:1-6. 2. Roche Diagnostics. *CoaguChek System: Why Use?* Available at: http://www.coaguchek-usa.com/information_for_professionals/why_use/content.html. Accessed May 12, 2006. 3. Wittkowsky AK et al. *Pharmacotherapy.* 2005;25:265-269.

Key take home points . . .

- Oral anticoagulants are labor intensive to manage
- Expert dose and patient management are key factors in success
- Specialized programs – AMS or ACC – have been shown to provide such expert care
- Maintaining time in range and good patient communication are key factors for success
- The key elements of such programs are adaptable to small physician offices where only a few patients are managed
- Further improvement in outcomes can be achieved by initiating POC patient self-testing or self-mangement

How could this patient have been managed better . . .

A 71 year old male was started on warfarin for an embolic CVA related to atrial fibrillation. He was discharged after being switched from heparin to warfarin with an INR of 2.1 on the day of discharge. An INR 4 days later was 2.8. His next INR was ordered for 3 weeks later; he obtained the INR in the morning and went home waiting for the call. Later that day, at home, he was found comatose. The INR pending from the morning was 14.6. The patient was found to have a massive intracranial hemorrhage and he subsequently died.

Even without knowing more information about this case, what went wrong? There are at least 2 management deficits, both of which could have been avoided.

Questions?