La gestione della terapia con AVK nei pazienti con insufficienza renale avanzata

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anticoagulation. Patients with renal failure on new anticoagulants have experienced excessive bleeding which can be related to a changed pharmacokinetic profile of the compounds. However, the coagulation system itself, even without any interference with coagulation modifying drugs, is already profoundly changed during renal failure. Coagulation disorders with either episodes of severe bleeding or thrombosis represent an important cause for the morbidity and mortality of such patients. The underlying reasons for these coagulation disorders involve the changed interaction of different components of the coagulation system such as the coagulation cascade, the platelets and the vessel wall in the metabolic conditions of renal failure. Recent work provides evidence that new factors such as microparticles (MPs) can influence the coagulation system in patients with renal insufficiency through their potent procoagulatory effects. Interestingly, MPs may also contain microRNAs thus inhibiting the function of platelets, resulting in bleeding episodes. This review comprises the findings on the complex pathophysiology of coagulation disorders including new factors such as MPs and microRNAs in patients with renal insufficiency.

such new compounds. A major problem is the prolong
life of some new substances due to pharmacokinetic
namely accumulation of the compounds during renal
Moreover, even without coagulation-modifying com
the function of the coagulation system itself is
profoundly changed in patients with renal failure, as
prone to episodes of prolonged bleeding. On the othe
they may also develop excessive formation of thror
Bleeding disorders are the result of insufficient fun
platelets, the coagulation cascade and/or activation
fibrinolytic system, while hypercoagulability is rather tl
of disorders of the coagulation regulatory factors
as platelet hyperreactivity [1, 2]. Little is known
about the reasons why one patient develops bleedi
blems, while another tends to head towards excessive
bus formation. However, both problems are of sig
clinical relevance as some patients can be endangered
bleeding episodes such as prolonged bleeding from the
fistula, gastrointestinal bleeding or cerebral haem
while other patients experience a prothrombotic status
ated with an increased number of cardiovascular ev

toma, epistaxis, haematuria, ecchymosis, purpur
from the gums, gingival bleeding, genital bleeding, h
telangiectasia, haemarthrosis and petechiae (Table 1

What could be the pathophysiological basis
creased risk of bleeding in patients with renal failur

Platelets

It has been shown that the platelet function is
in patients with severe renal impairment [1, 5]. A
nized abnormality in platelet physiology contributi
let dysfunction with bleeding problems in patients
failure is the disturbance of the platelet α-granul
They contain platelet factor 4, transforming growt
platelet-derived growth factor, fibronectin, B-thro
lin, von Willebrand factor (vWF), fibrinogen, ser
coagulation factors V and XIII. In uraemic patie
granules have an increased ATP/ADP ratio and
content of serotonin. Furthermore, the thrombi
release of ATP together with an increased calcium
a disturbed intracellular calcium flux upon several
been related to platelet dysfunction and bleeding
patients [11]. Platelets of uraemic patients also de

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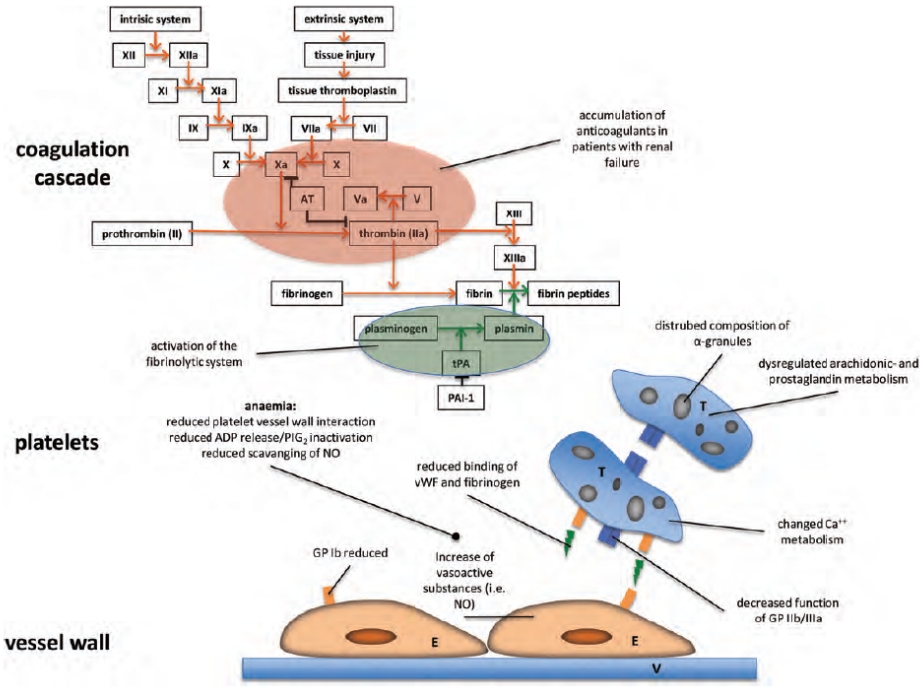
Bleeding in renal failure



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Thrombosis in renal failure

histomorphologic diagnosis should be confirmed by biopsy. A definitive treatment can be achieved if treatment of the underlying renal disease with a substantial reduction of the proteinuria is successful.

Heparin-induced thrombocytopenia type II (HIT II)

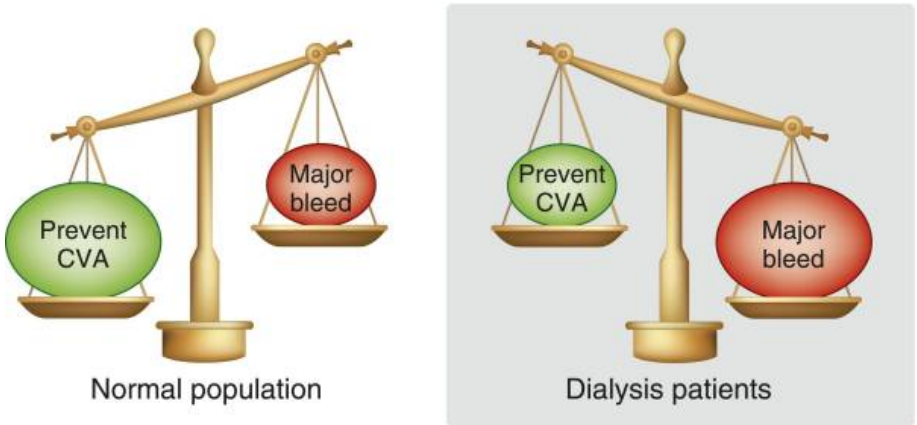
HIT II is a prothrombotic state related to the formation of platelet-activating antibodies that are directed against complexes of platelet factor 4 and heparin. Despite low platelets HIT II leads to thromboembolic events (venous > arterial thromboembolism) in 50–60%. Patients on dialysis are at particular risk for the development of HIT II as they receive heparin as an anticoagulant during dialysis at a regular basis. However, HIT II is not as frequent among patients receiving HD as one might suggest with a reported frequency between 0.5 and 3–5% [89]. The incidence is strongly influenced by the nature of the heparin fraction, the dosage and the duration of administration. After administration of LMWH, the HIT II-incidence is 10 times lower than after administration of unfractionated heparin. The HIT II-incidence depends furthermore on patient-related factors (surgical patients > medical patients). Interestingly, the risk for development of HIT II is low in non-surgical populations (critically ill patients and patients receiving HD) and very low in pregnant women [89, 90]. Platelet-activating antibodies (HIT-II-antibodies) do not necessarily lead to clinically apparent I
not clear what makes an individual suscep
opment of platelet-activating antibodies anc
do only a minority of these patients with
develop a clinical manifest HIT II [91]. Hc
seem that the renal insufficiency itself or ur
role in this respect. If anticoagulation m
patients with HIT, argatroban or regional
tion may be used as alternative anticoagul
parins. Danaparoid (HIT II could progress
danaparoid), lepirudin (has been taken fr
fondaparinux (not licensed for HIT II ther
used in patients with renal failure as they
accumulate in these patients. The new oral
bigatran, rivaroxaban and apixaban are
patients with ESRD (ESC Clinical Practice
2012). Dabigatran can be eliminated via H
dosing with severe bleeding complications.

Anticoagulation strategies during haem

Unfractioned heparin (UFH) is not a sir
composition of more than 120 different
them different glycosaminoglycans consisti
glucosamine and D-glucuronic acid units.
logical purity cannot be determined. It

Lutz J et al, *Nephrol Dial Transplant* 2014;29:29-40

Advanced renal failure



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The prevalence of AF was 11.6% and the overall incidence was 2.7/100 patient-years. The risk of mortality and stroke was increased in ESRD patients with AF at 26.9 and 5.2/100 patient-years versus 13.4 and 1.9/100 patient-years compared with ESRD patients without AF. The majority of studies do not support a protective effect for warfarin in ESRD patients with AF.

Conclusions. The incidence and prevalence of AF in ESRD patients are higher than in the general population and are associated with an increased risk of stroke and mortality. An appropriately designed randomized controlled trial is required to determine whether anticoagulation is an appropriate therapeutic strategy in patients with end-stage renal disease and atrial fibrillation.

Keywords: atrial fibrillation; hemodialysis; mortality; prevalence; stroke

prevalent in people with ESRD, so that the majority patients would require warfarin anticoagulation for the AF based on their $CHADS_2$ score. However, we have shown previously that patients with ESRD are at an ~1 fold increased risk of bleeding compared with the general population when treated with warfarin [5]. We have also shown an increased risk of valvular calcification in patients with ESRD on a long-term warfarin therapy [3]. Thus, the risk-benefit ratio of warfarin therapy is uncertain in patients with ESRD despite the high CHADS score in this population.

Given the potential equipoise experienced by clinicians managing patients with ESRD and AF, we performed a systematic review to summarize what is known of the incidence and prevalence of AF, and the risks of mortality and stroke, treated or untreated with warfarin or antiplatelet agents.

Fig. 2. Prevalence of atrial fibrillation in patients with ESRD.

was paroxysmal [18]. The importance of paroxysmal AF should not be underestimated, as demonstrated in the study by Chou *et al*. in which this form of the arrhythmia was associated with the greatest risk of stroke [21]. In anticoagulation guidelines for the general population, no distinction is made AF.

There is also a tre prevalence of AF (11 16–27, 29, 30, 33]. I

Fig. 4. Mortality in patients with ESRD with and without atrial fibrillation.

design mentioned above, the technique used to diagnose the arrhythmia was different across the studies. In some cases, there is no mention of how patients were monitored, whereas in other studies monthly electrocardiograms or 24-h Holter monitoring were used which would potentially identify asymptomatic individuals [24]. Some

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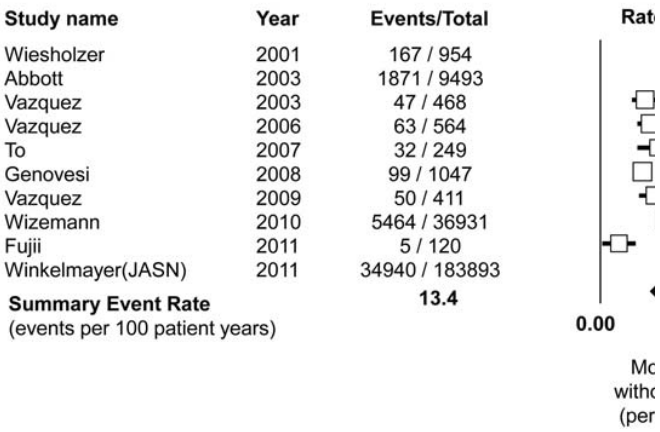
Zimmerman D et al, *Nephrol Dial Transplant* 2012;27:3816-3822



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to mortality for the same patients. For the same reason, cross-sectional studies reporting prevalence may have different estimates than retrospective or prospective cohort studies in which 'prevalence' incorporates incidence.

The estimated risks and benefits of anticoagulation for patients with ESRD and AF remain unclear. Overall, patients with ESRD experience a 5–10-fold higher rate of ischemic and hemorrhagic stroke compared with the general population: the risks and benefits of intervention are likely to be very different [34]. In our review, the highest risk of thromboembolism is reported in the studies by Vazquez *et al*. in which they have quoted a 4.6, 5.2 and 9.8-fold increased risk associated with AF [27–29]. However, this group of investigators included systemic embolism and transient ischemic attacks, which were not included in the other studies. Furthermore, the diagnosis of TIA is often clinical and may be prone to subjective clinical interpretation. The 9.8-fold increased risk was based on a total of seven ischemic strokes over 4 years of which 2 occurred in patients who did not have AF. The small number of events affects the stability of the estimates. The use of anticoagulants and the incidence of hemorrhagic stroke were not discussed. In the study by Chan *et al*. in which all patients had AF, 44.7% of patients were on warfarin, 11.4% on clopidogrel and

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to develop a focused understanding for the indications for warfarin, clopidogrel, and aspirin prescription for patients with ESRD, we performed a follow-up study to determine the potential risk-benefit ratio of these drugs specifically in dialysis patients with coexisting atrial fibrillation.

The population of patients with atrial fibrillation is heterogeneous[13–16] in terms of risk for stroke, and the hazards of anticoagulation may outweigh its

patients without renal failure.[2,36] Given th

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terms among warfarin, clopidogrel, and aspirin were not found to be significant when included in the Cox model.

Secondary Stroke Analysis

Implementation of propensity scoring did not significantly alter the findings of the primary analysis. A statistically and clinically significant association between warfarin use (*versus* nonuse) and increased stroke remained even when the propensity score was added as a covariate to the model (Table 2) or in a propensity-matched subcohort (HR 2.00; 95% CI 1.32 to 3.04 in 746 warfarin users matched to 746 nonusers with a similar propensity score).

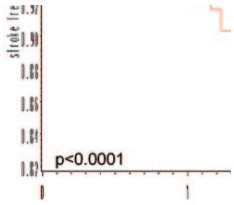

Figure 1. Crude stroke curve assumption, increased incidenc on warfarin. (B) Similar results changed their warfarin, clopido

When compared with patients who were not on the drug, warfarin increased the risk for new stroke regardless of whether a patient had congestive heart failure, hypertension, an age >75 yr, previous stroke/transient ischemic attack (TIA), or diabetes. Although warfarin use was also associated with an increased risk for new stroke in all $CHADS_2$ strata, the margin between the risk and benefit decreased with increasing $CHADS_2$ score (Figure 2). Thus, the risk associated with warfarin use was reduced in patients who had atrial fibrillation and were at high risk for future stroke (higher $CHADS_2$ score) relative to those at low risk, which is consistent with treatment guidelines in the general population.[39,40] When analyzed separately, the adjusted ischemic stroke HR with warfarin use (*versus* nonuse) was 1.81 (95% CI 1.12 to 2.92; Figure 2), whereas the risk for hemorrhagic stroke with warfarin use was

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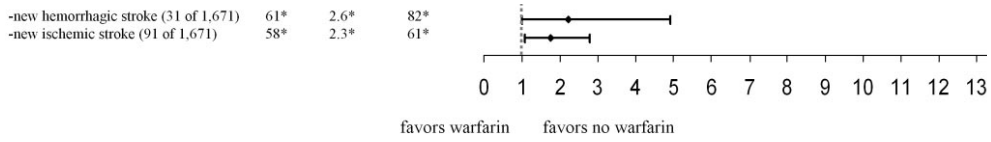

Figure 2. Stratified analysis. Patients at higher risk for future stroke (higher $CHADS_2$ score) had better risk-benefit pr (warfarin*$CHADS_2$ = 0.84; P = 0.31 for interaction) with warfarin use when compared with nonusers. With the exception of diab there were no statistical differences in the prevalence of warfarin use, INR level, or INR monitoring with increasing risk for s ($CHADS_2$ score) and by five well-established risk factors for future stroke in atrial fibrillation.[38] The crude ischemic stroke rate in wa users was 5.8 strokes per 100 patient-years (95% CI 4.6 to 7.4) *versus* 2.3 strokes per 100 patient-years in nonusers (95% CI 1.5 to The crude hemorrhagic stroke rate in warfarin users was 1.2 strokes per 100 patient-years (95% CI 0.7 to 2.1) *versus* 0.5 strokes pe patient-years in nonusers (95% CI 0.2 to 1.4).
†Statistically significant difference (P = 0.03) in prevalence of warfarin use in diabetic *versus* nondiabetic incident dialysis patients atrial fibrillation.
§As expected, patients with a higher propensity for warfarin prescription had a higher prevalence of warfarin use.
¥After matching, the caliper width of the propensity score between the two groups was found to be ±0.6 SD.
*Values reported only for patients who had a stroke outcome.
CHF, congestive heart failure; HTN, hypertension.

that was found in this study may seem to challenge general recommendations for stroke prevention, several clinical studies indirectly support this reassessment of the relative risk-benefit ratio for anticoagulation use in dialysis patients.[2] the US Renal Data System reported a 10-fold increase in subdural hemorrhages in dialysis patients (although their medication was not specified) when compared with nondialysis patients,[43] whereas a review of 28 studies of warfarin use in dialysis patients suggested its use doubled the risk for major bleeding.[44]

Treated hypertension,[18–20,45,46] cerebrovascular disease,[23] emic stroke,[21,47] serious heart disease,[23] renal insuffi cy,[23,48–50] and advanced age[25,49,51–53] have been reported t tentiate bleeding during warfarin therapy and are highly prev in the dialysis population. Our study also suggests that war users with no in-facility INR monitoring had the greatest ris stroke, and hemorrhagic complications may be minimized frequent monitoring and tight management of a patient's an agulation status.

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Parameter	(*n* = 746)	(*n* = 925)		
	Total Deaths (Deaths per 100 Patient-Years)		*n*	HR (95
HR for mortality				
unadjusted model	333 (27.4)	425 (25.7)	1671	1.03 (0.89
covariate adjusted model			1671	1.10 (0.94
covariate and propensity score adjusted model			1400	1.10 (0.93
death from stroke	16 (1.3)	6 (0.4)	1400	4.31 (1.44
death from cardiovascular disease	205 (16.9)	265 (16.5)	1400	1.04 (0.85
death from bleeding	5 (0.41)	6 (0.37)	1400	1.24 (0.26
death from infection	24 (2.0)	41 (2.6)	1400	0.87 (0.48
other causes of death	83 (6.8)	107 (5.8)	1400	1.22 (0.89

Chan K E et al, *J Am Soc Nephrol* 2009;20:2223-2233

Evaluation, Faculty of Medicine, University of Toronto, Toronto, Canada; Division of Cardiology, Schulich Heart Centre, Sunnyl Centre, University of Toronto, Toronto, Canada (J.V.T.); and Institute for Clinical Evaluative Sciences, Toronto, Ontario, Canada (H

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Table 3. Association between Warfarin Use and the Risk for Stroke and Bleeding Fibrillation

Patients With AF	Outcomes	Adjusted* HR (95% CI)	Propensity
Dialysis (n=1626)	Stroke‡	1.14 (0.78–1.67)	
	Bleeding§	1.44 (1.13–1.85)	
Nondialysis (n=204 210)	Stroke‡	0.87 (0.85–0.90)	
	Bleeding§	1.19 (1.16–1.22)	

AF indicates atrial fibrillation; CI, confidence interval; HR, hazard ratio; NSAIDs, nonsteroidal anti-i transient ischemic attack.

*Stroke outcome was adjusted for age (years), sex, specific components of $CHADS_2$ stroke prediction s hypertension, diabetes mellitus, and history of stroke/TIA).

*Bleeding outcome was adjusted for: age (years), sex, specific components of HAS-BLED bleeding p hypertension, history of stroke/TIA, history of bleeding, and use of aspirin, clopidogrel, or NSAIDs).

†Propensity score was derived from the following variables: age ≥75 y, sex, type of AF (primary vs s and ≥2), liver disease, congestive heart failure, hypertension, diabetes mellitus, history of stroke/TIA, h control drug, rhythm control drug, aspirin, clopidogrel, and NSAIDs.

‡Stroke was defined as the first hospital admission or emergency department visit for ischemic cer retinal infarct at any point during the follow-up period.

§Bleeding was defined as the first hospital admission or emergency department visit for intracerel bleeding, intraocular bleeding, hematuria, and unspecified location of bleeding at any point during the fo

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allowed us to study the association between warf
the risk for stroke and bleeding in the AF cohort.
studies, we attempted to reduce concerns about sta
fitting[46] and included only the most relevant cova
adjusted analyses. Finally, the information availab
large Quebec and Ontario healthcare databases ref
clinical practice in Canada and may be less prone
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patients irrespective of whether they have AF, su
that warfarin use by HD patients may be hazardous
16]. Furthermore, Shah et al. reported that warfarin
did not reduce stroke risk, but increased the risk of
bleeding [17]. Olesen et al., on the other hand,
finding that non-valvular AF patients on renal repl
therapy were at higher risk of stroke and

age but not between death from any cause and warfarin; however, antiplatelet use was also significantly associated with death from any cause.

The results for composite events, which include death from any cause, stroke, cardiovascular disease, and peripheral arterial disease, are shown in Table 3. The

from any cause and composite events, warfarin
associated with the internal bleeding (Table 3).
also associated with the risk of internal bleeding

The results of the multivariate Cox analysis for
shown in Table 4. The results for all of the pat
whole showed that antiplatelet drug as well as

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of the risk factors showed a significant association for hemorrhagic stroke (data not shown).

The results of the multivariate Cox analysis for cardiovascular disease showed a similar finding to the results for

increases in death from any cause, composite e
internal bleeding. In this analysis, age and hist
betes mellitus were significantly associated
from any cause and composite events.

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trary, it seems likely that patient who had higher risk for ischemic stroke had received antiplatelet drugs, and therefore an association between antiplatelet use and outcomes cannot be interpreted as a causality. On the other hand, none of the risk factors showed a significant association for hemorrhagic stroke (data not shown).

The results of the multivariate Cox analysis for cardiovascular disease showed a similar finding to the results for

was relatively low, while it was within therape
recommended by the Japanese Circulation Societ
shown in Table 5, higher PT-INR values in the
fourth quartile were not significantly associated
increases in death from any cause, composite e
internal bleeding. In this analysis, age and histo
betes mellitus were significantly associated w
from any cause and composite events.

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The decision to anti-coagulate or use anti-platelet therapy in a patient with AF requires consideration of potential harms *versus* benefits. Such harms and benefits have been established for the general population through multiple large randomized controlled trials (RCT).[11–13] These data have been used to power predictive scores, the $CHADS_2$ (Cardiac failure, Hypertension, Age, Diabetes and Stroke) and more recently the CHA_2DS_2-VASc (Cardiac failure, Hypertension, Age, Diabetes, Stroke, Vascular disease and gender) scores,

uraemia, altered pharmacokinetics and increased risk.[16,17] There are also concerns that the use of warfa haemodialysis patients may increase vascular calcifi and hence, ischemic stroke risk.[16,18] Although there ar oral anticoagulants on the market, none of thes approved for use in dialysis patients and so are not exa in this paper.[19]

No RCT of anti-coagulation or anti-platelet int tions in haemodialysis patients with AF have

were drawn from the literature.

786

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sensitivity analysis was 2.39 years for no therapy, 2.36 years for aspirin and 2.37 years for warfarin. For the outcome of life expectancy 67% of simulations favoured no treatment, 33% of simulations favoured aspirin and 0% of simulations favoured warfarin. The mean QALY for the probabilistic sensitivity analysis were 1.61 years for no therapy, 1.61 years for aspirin and 1.47 years for warfarin. For the outcome of quality-adjusted life expectancy, 62% of simulations favoured no treatment, 38% of simulations favoured aspirin and 0% of simulations favoured warfarin. In summary, in 100% of simulations for survival and 100% of simulations for QALY, warfarin was not the preferred treatment choice for AF in haemodialysis patients given the current evidence base.

warfarin, aspirin and no therapy is small and is overwhelmed by the poor prognosis of these patients regardless of anti-coagulation/anti-platelet therapy. We caution that our findings may not be applicable to patients that differ significantly from this base case, for example, those who are much younger or have valvular AF. Analysis of such patients is not possible due to lack of evidence on their outcomes in the literature.

A decision analysis has been previously conducted by Quinn *et al*.[47] They found that warfarin produced an additional 0.1 years of life expectancy and an additional 0.1 QALY *versus* no therapy and was superior to both no therapy and aspirin.[47] Since this publication, a number of important studies have reported stroke and bleeding rates in haemo-

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Subject Heading terms "atrial fibrillation," "warfarin" and "bleeding" were combined with "end-stage renal disease," "dialysis," and "kidney failure." Studies that assessed warfarin use in patients undergoing hemodialysis with a target international normalized ratio of 2 to 3 were included for review.

Prevention of thromboembolic events, particularly stroke in patients with atrial fibrillation from the general population, is associated with substantial reduction in morbidity and mortality.[3] A numb-

Renal Data System 2008 report,[40] the averag
an incident dialysis patient is 64.4 years, v
fastest growing population being those ≥ 75
age (65% rate increase since 2000). Factors
tive of increased bleeding, such as diabetes
(44.8%) and hypertension (27%), are the mc
mon causes of ESRD. Vitamin K deficiency
ary to malnutrition, frequent antibiotic u
abnormal cholesterol metabolism may lead
tuations in responsiveness to OAC.[41] Finally
such as quality of life, a wish for decreased
procedures and interventions, and decrea
burden may tip the decision in favor of not
agulating.