

PRACTICAL POINTERS
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MAY 2011

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EDITED BY RICHARD T. JAMES JR. MD

400 AVINGER LANE, SUITE 203

DAVIDSON NC 28036 USA

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Rjames6556@aol.com**

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This document is divided into two parts

1) The **HIGHLIGHTS AND EDITORIAL COMMENTS SECTION**

HIGHLIGHTS condenses the contents of studies, and allows a quick review of pertinent points of each article.

EDITORIAL COMMENTS are the editor's assessments of the clinical practicality of articles based on his long-term review of the current literature and his 25-year publication of *Practical Pointers*.

2) The main **ABSTRACTS** section is designed as a reference. It presents structured summaries of the contents of articles in much more detail.

I hope you will find *Practical Pointers* interesting and helpful. The complete content of all issues for the past 10 years can be accessed at www.practicalpointers.org

Richard T. James Jr. M.D.

Editor/Publisher.

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HIGHLIGHTS AND *EDITORIAL COMMENTS* MAY 2011

One Of The Most Important Sources Of Clinical Uncertainty.

5-1 FROM EFFICACY TO EFFECTIVENESS IN THE FACE OF UNCERTAINTY

Clinical research is typically performed to address questions of:

- 1 Efficacy: Can it work in ideal settings?
2. Effectiveness: Does it work when generalized to the real-world and applied to individual patients?
3. Cost effectiveness: Is it worth it, and should it be paid for?

To date, research has been dominated by efficacy. It is not possible to provide reliable empirical evidence of effectiveness and cost-effectiveness on every question to guide decision-making. Instead, practitioners will continue to rely on inductive reasoning to apply the results of a study (“group averages” from efficacy trials) to individual patients who often differ in important ways from patients entered into efficacy trials. (Eg, patients may be older, have comorbid conditions, and using multiple medications.)

An insolvable problem then arises because there is no guarantee that the treatment effect observed in one group of patients can be repeated with certainty in a future patient. Decades of clinical experience have demonstrated that application of group trial data to individual patients is permissible by using efficacy as effectiveness data—provided there is a rationale for exchangeability of the past (the trial subjects) and future (your patient) events and the characteristics and circumstances of the subjects and the patient are sufficiently similar.

But, there is no precise resolution of what constitutes “sufficiently similar”. Determination of similarity is often based on PICO: Whether characteristics between subjects in a trial and your patient are similar enough to allow application of the trial results to individual patients in real world settings. This is a matter of judgment.

Patients (P)

Interventions (I)

Comparators (C)

Outcomes (O)

Relying on efficacy data to draw conclusions about effectiveness and the feasibility of application of trial data to an individual patient remains one of the most important sources of clinical uncertainty.

Indication creep:

Uncertainty is a key driver of the well-documented variations in the practice of medicine. Such variations commonly occur via so-called indication creep—the practice of promoting the use of an intervention for off-label indication. It is pervasive. When regulatory agencies approve a new drug, physicians are at liberty to administer the drug outside the approved indication provided they believe that doing so will benefit the patient.

Many off-label uses have been shown to have little or no scientific support. Indication creep is also inextricably linked to promotion of drugs by profit-driven industries.

Various mechanisms can lead to indication creep: Reducing the threshold for diagnosis, relying on surrogate endpoints, exaggerating efficacy and safety claims, and disease mongering. At its core, indication creep represents a shift from efficacy to effectiveness in an attempt to tailor research evidence to individual patients.

Prevention creep: The promotion of tests developed to detect symptomatic disease in asymptomatic patients.

For example:

When statins, which have proven highly beneficial in secondary prevention of heart disease, are extended for primary prevention in a population at low risk of heart disease.

When prostate specific antigen, which is important for detection of prostate cancer in symptomatic patients, is used for cancer screening.

When computed tomography, which is highly effective for cancer staging in patients with known disease, is promoted for detection of tumors in asymptomatic patients.

When chemotherapy, which is effective in management of advanced stages of cancer such as lymphoma or chronic lymphocytic leukemia, is increasingly used for treatment of minimal residual disease.

Uncertainty, Inescapable errors, Unavoidable Injustice

Judgments applied to extrapolation of evidence to individuals beyond the published limits of clinical trial data are inherently fraught with uncertainties. As a consequence, such extrapolation will not always be appropriate, resulting in inevitable error. Errors related to indication creep are typically:

- 1) False-positive error leading to *overuse* of health care interventions. (Inappropriate application of trial data to individual patients.)
- 2) False-negative error, resulting in *underuse* (failure to use an effective intervention).

Clinicians regret the consequences of unnecessary treatments (regret commission) less than the consequences of not administering treatments which would benefit (regret omission).

Overuse of health care interventions leads to squandering precious and finite resources. Because resources used for one group of patients cannot be used for another, indication creep inevitably leads to an increasing in health inequities and social injustice, and creates an acute ethical societal dilemma.

By decreasing false-positive error (*overuse*), social injustice can be minimized—distributing scarce health resources according to the principle of utilitarianism, emphasizing “the greatest good for the greatest number”. However, this will lead to unavoidable individual injustice resulting from an increase in false-negative error (*underuse*) because those patients who might benefit from the appropriate use in off-label settings, or the administration of screening tests, will not receive them.

Indication Creep Belongs to the “No Technical Solution” Class of Problems

At present 30% of health care is inappropriate or wasteful. Given that 100% accurate decision-making is not possible, and that uncertainty, including error, must be considered facts of life, can the current situation be improved?

Curtailing commercial influence on prescribing and more comparative effectiveness research closely matched to PICO characteristics with individual-patient characteristics can help reduce indication creep. But physicians will never obtain empirical answers to all questions for caring for the patient. Physicians will always need to extrapolate beyond available evidence in their attempts to tailor treatments to individuals.

There is no technical solution to the ethical dilemma posed by indication creep. Any solution requires explicit consideration of the social values associated with the consequences of false-positive and false-negative errors. Any action may affect different individuals differently.

In the context of current indication creep, the public must understand that physicians are much more willing to tolerate false-positive errors (*overuse*) than false-negative error (*underuse*).

At present, squandering health resources appears to be more palatable than potential injustice to individuals by *underuse*.

JAMA May 18, 2011; 305: 2005-06 Commentary, first author Benjamin Djulbegovic, University of South Florida, Tampa

This is a thoughtful and important article. It describes the present state of primary care. It discusses the “art “ of medicine-- the application of medical science to individuals, all different.

We cannot predict effectiveness to individual patients. They will vary in some ways (perhaps in most ways) from subjects entered into trials.

Trials often report benefits as a percentage of the subjects entered. If only 10% of subjects benefited in a trial, how can we predict which individual patient will benefit?

Cost effectiveness is often neglected in individual patients. Does the prescriber know the cost of the drugs he prescribes? Can the patient afford it? The best application of evidence-based medicine and the best of drugs are meaningless if the patient cannot afford them.

Primary clinicians must know as much about the characteristics of individual patients as they know about their disease and the applicable trials.

Can this treatment help my patient?

What is the probability it will help?

What is the harm?

How much does it cost?

Immediate Treatment Is Urgent; Application Of Appropriate Treatment Is Often Low.

5-2 MEDICAL TREATMENT IN ACUTE AND LONG-TERM SECONDARY PREVENTION AFTER TRANSIENT ISCHEMIC ATTACK AND ISCHEMIC STROKE.

Although primary prevention is most important, secondary prevention is essential. Recurrent strokes are common, more severe than first strokes, and are more likely to cause dementia.

This review considers the evidence that led to this improvement in outcome. It is confined to the medical treatments that should be considered for most patients with TIA or IS.

Acute secondary prevention:

Secondary prevention should be started urgently after a TIA or minor stroke. A meta-analysis reported that stroke risk is 3.1% at 2 days and 5.2% at 7 days.

Acute treatment after TIA or minor stroke:

Urgent treatment within 1 day improves prognosis. A delay in treatment of 20 days was associated with a 10% risk of stroke vs 2% when treatment was started at day one.

Early administration of aspirin is beneficial. But guidelines still recommend aspirin + dipyridamole (*Aggrenox*) or clopidogril as first-line treatment. Clopidogril + aspirin is more beneficial than aspirin alone, but at increased risk of bleeding.

Antihypertensive drugs:

BP often rises shortly after a TIA or stroke. It tends to fall spontaneously during the first few days. Falling cerebral perfusion is less likely to be a concern after a TIA or minor stroke. Many clinicians start BP therapy immediately. It is not associated with a higher risk of stroke

Long-term secondary prevention:

Antiplatelet; anticoagulant

Appropriate use of anti-platelet drugs and anti-coagulants depends on whether the underlying cause is cardio-embolic or presumed arterial origin.

Arterial origin TIA or stroke

Aspirin is recommended for secondary prevention when the cause is arterial.

Guidelines still recommend aspirin + dipyridamole (*Aggrenox*) or clopidogril as first-line treatment. Vitamin K antagonists (eg. warfarin) are *not* recommended.

Use is associated with increased intracranial hemorrhage.

Cerebral ischemia of cardiac origin:

About 20% of all TIA and ischemic stroke have a cardiac origin, most commonly with atrial fibrillation. (**AF**) . In patients with a recent TIA or ischemic stroke of cardiac origin, vitamin K antagonists (eg, warfarin) are preferred. Aspirin is of some value in patients who are ineligible for warfarin. Aspirin + clopidogril is *not* as effective as warfarin.

A trial of the direct thrombin inhibitor dabigatran 150 mg daily found fewer ischemic events with the same risk of hemorrhage as warfarin. A trial of a factor Xa inhibitor apixaban vs aspirin found a relative risk of primary outcome events of 0.45. Current guidelines still recommend warfarin as standard treatment in patients

with AF. Long-term safety of the newer anticoagulants and their costs require further study.

Lipid modification

Statin drugs are effective. A reduction in LDL-cholesterol to 70 mg/dL was associated with a 28% greater reduction compared with a reduction to 100.

Antihypertensive drugs:

Hypertension (especially systolic) is the most important modifiable risk factor for stroke prevention, particularly in elderly people. A meta-analysis showed that reductions in BP lowered risk of recurrent stroke by 26%. A larger reduction was associated with greater benefit. Current guidelines recommend treatment with BP-lowering drugs in most patients with a history of TIA or stroke.

Potential long-term benefit of aggressive multi-risk factor control:

If one uses the observed treatment effect from randomized trials and assumes that the relative effects of each treatment are independent of the others, treatment of all major risk factors is estimated to reduce risk of recurrent stroke by 80%.

Conclusion: Secondary treatment with antiplatelet agents, antihypertensives, statins, and anticoagulation, and carotid endarterectomy as appropriate, should be initiated urgently after TIA or minor stroke. The risk of recurrent stroke is high. For long-term secondary prevention, most guidelines recommend aspirin plus dipyridamole or clopidogril for cerebral ischemia of arterial origin. For cardiac origin, factor Xa inhibitors and thrombin inhibitors are challenging the current standard of vitamin K antagonists. Lipid-lowering and antihypertensive treatments are warranted after both types of cerebral ischemia (arterial and cardiac).

This is the UK view. It is straightforward and simple. The article did not elaborate on carotid endarterectomy.

All primary care clinicians are aware of these interventions. The challenge is to apply them promptly and long-term. The interventions apply to primary prevention as well.

See the full abstract.

MmolHbA1c/mol Hb A

5-3 HbA1c: AN OLD FRIEND IN NEW CLOTHES

The units of HbA1c have changed.

The way in which we use and interpret glycated hemoglobin A1 measurement is also changing. New guidances for the diagnosis of diabetes include HbA1c.

HbA1c was discovered in the 1960s through the electrophoresis of hemoglobin. Routine measurement was applied into clinical practice in the 1990s after the Diabetes Control and Complications Trial (DCCT).

The use of HbA1c in the diagnosis of diabetes is controversial, although a 2009 expert consensus strongly advocated measurement of it for this purpose.

The International Federation of Clinical Chemists (IFCC) has altered the units in which HbA1c is reported by replacing the traditional percentage units with standard mmolHbA1c/mol Hb A (mmol/mol) measurement. This may be confusing.

Why the change? Lack of agreement of HbA1c among laboratories has long been a concern. A reference method remained undefined. The IFCC has produced a purified preparation of HbA1c, which enabled development of a reference method.

The new preparation showed a 1.5% to 2% lower HbA1c level than the traditional HbA1c. This discrepancy may result in patients and clinicians mistakenly believing that glycemic has improved. To reduce confusion, the ISCC has changed its unit of measurement from percentage to mmol of HbA1c per mol of hemoglobin A (mmol/mol).

Clinicians should resist converting mmol/mol back to DCCT-aligned percentage units. This comparison should be used only to educate patients about the key target in the new units –less than 6.5% of HbA1c becomes less than 48 mmol/mol.

The DCCT-aligned results are now effectively meaningless.

In 2009, the American Diabetes Association and the WHO proposed HbA1c as a diagnostic criterion for diabetes, suggesting a cut-off greater than or equal to 48 mmol/mol as being diagnostic.

One untimed, non-fasting blood sample has clear advantages. HbA1c concentration varies less within the same individual than fasting glucose or the glucose tolerance test.

However, HbA1c is affected by red-cell turnover (anemia), age, ethnicity, and genetic polymorphisms. The assay is also subject to interference from hemoglobin variants (sickle cell) and derivatives resulting from renal failure and drugs.

Can HbA1c concentrations below a given threshold exclude diabetes on the basis of one sample in an individual with unknown hemoglobin phenotype and unknown renal or iron status? Potential interference needs to be identified. The trend in HbA1c, rather than the absolute value, is of primary interest when HbA1c is used for glycemic monitoring. It is crucial to identify these interferences when a single HbA1c is used for diagnosis.

In June 2011, the DCCT units will cease to be co-reported.

It is time to reset our minds.

Lancet April 30, 2011; 377: 1476-77 First author Shivoni Misro, Imperial Health NHS Trust, London, UK

Equivalent DCCT-aligned and IFCC-standardized values:

DCCT (%)	IFCC (mmol/mol)
5	31
6	42
7	53
8	64
9	86
10	108

I have yet to see any mention of the new standards in the articles about diabetes I abstract. What now is the place of fasting blood glucose? Is the glucose tolerance test obsolete? What about home glucose monitoring?

5-4 ANTICOAGULANT OPTIONS—WHY THE FDA APPROVED A HIGHER BUT NOT A LOWER DOSE OF DABIGRATRAN

In October 2010, the FDA approved dabigatran for the reduction of stroke and systemic emboli in patients with non-vascular atrial fibrillation (AF). Approval was based on the RE-LY¹ study, which randomized patients to dabigatran 150 mg twice daily; dabigatran 110 mg twice daily; and warfarin titrated to an international normalized ratio (INR) of 2.0 to 3.0.

Primary endpoint was stroke or systemic embolism

Both doses were non-inferior to warfarin in prevention of stroke and in risk of bleeding.

The 150 mg dose was significantly superior to warfarin in preventing stroke. Risk of bleeding was slightly less.

The 110 dose was associated with less bleeding than the other 2 drugs. Risk of stroke was slightly higher than the 150 dose.

Both doses would have been considered safe and effective if each of the doses were used alone in comparison to warfarin. In the end, the FDA approved only the 150 mg dose as showing clear superiority.

Patients and physicians value choice that allows treatment to be individualized. In patients for whom there is reason for heightened concern about bleeding, the low dose might have seemed desirable, even at the cost of higher risk of stroke.

Patients with impaired renal function (especially the elderly in whom AF is more common) have higher dabigatran blood levels and may be predisposed to bleeding. The low dose might offer advantages in these patients. Most people would agree that the irreversible effect of stroke has a greater clinical significance than nonfatal bleeding.

Warfarin is widely underused in patients with AF for a number of reasons including difficulty maintaining an INR within therapeutic range. Some may be willing to use dabigatran.

Efficacy and major safety outcomes in RE-LY

	110 mg (n = 601)	150 mg (n = 607)	Warfarin (n = 602)
% per year			
Stroke or systemic emboli	1.5	1.1	1.7
Stroke Ischemic	1.3	0.9	1.1
Hemorrhagic	0.1	0.1	0.4
Systemic emboli	0.1	0.1	0.2
Major bleeding	2.9	3.3	3.6
Life threatening bleeding	1.2	1.5	1.9
Hazard ratio for stroke vs warfarin	0.74	0.52	
Hazard ratio for stroke 150 vs 110 = 0.72			

Practical Pointers has abstracted several articles concerning the new anticoagulants (Factor Xa inhibitors as well as thrombin inhibitors). It may take a while to compare the benefit / harm-cost ratio of the various drugs.

Should primary care clinicians now begin to use these drugs? I believe prudence is needed. We need more time to determine safety, dosage, adverse events, and drug interactions. They certainly look promising.

Pradaxa is available at local pharmacies at the 150 mg dose. Cost is \$278 for 60 tablets (one month's supply) —over \$3000 per year. It can be obtained at a dose of 75 mg on special order.

1 RE-LY: Randomized Evaluation of Long-term Anticoagulation Therapy

“Dabigatran vs warfarin in patients with atrial fibrillation” NELM 2010; 361: 1139-51
Dabigatran (*Pradaxa*; Boehringer Ingelheim) is a direct thrombin inhibitor. It is given by mouth. It has an advantage over warfarin in that it requires no monitoring, and is less affected by dietary factors,

Absorption may be delayed by proton pump inhibitor and when ingested with fatty foods.

Some drugs will raise the blood levels.

It has been studied in prevention of thrombo-embolic complications of orthopedic and other surgeries.

It performed as well as the low-molecular weight heparin, enoxaparin.

Source: Wikipedia

5-5 MORTALITY RISK AMONG MIDDLE-AGED WOMEN WITH FIRST ATRIAL FIBRILLATION

An article in this issue of JAMA¹ provides evidence of increased mortality risk among middle-aged women with new-onset atrial fibrillation (AF).

During a median follow-up of 15 years, 1011 women developed AF. Sixty three deaths occurred.

In multivariable models, incident AF was associated with an increased adjusted risk of all-cause, cardiovascular, and non-cardiovascular mortality.

The Framingham Heart Study (FHS) demonstrated that the development of AF was associated with attenuation of the female survival advantage. The present study confirms that AF is associated

with premature death. Newly identified AF in seemingly healthy women should be taken seriously, and treated aggressively, recognizing that anticoagulation reduces stroke and mortality risk.

Compared with women who remained free of AF, those who developed AF had higher prevalence of hypertension, diabetes, hypercholesterolemia, smoking, and body mass index (BMI). This represents a high-risk group. While the cohort was event-free at baseline, whether these women could be considered “healthy” is questionable.

Why the increased risk of death with AF? It may be due to increased heart failure, stroke, and myocardial infarction.

Structural abnormalities are common in persons with AF: Dilated left atrium, left ventricular hypertrophy. In a study of lone AF, patients with normal-size atria had a long-time benign clinical course. Patients with increased atrial volume experienced adverse events. Left atrial enlargement is the common denominator for the pathological cascade leading to stroke, heart failure, and death. While it is important to link AF to death in middle-aged women initially free of cardiovascular events, it is equally important to recognize that almost half of the women in the WHS cohort who developed AF had an enlarged left atrium, and a third had left ventricular hypertrophy—a high prevalence of structural changes.

The prevalence of AF is often underestimated. Clinically, AF detection is far from straightforward. When AF is paroxysmal, it may not be discovered.

From a public health standpoint, clinicians should be aggressive in detection and treatment of AF. Anticoagulation and hypertension control in patients with newly identified AF was shown to reduce stroke incidence.

JAMA May 25, 2011; 305: 2111-12 Editorial, first author Yoko Miyasaka, Kansai Medical University, Hirakata, Japan

1 RISK OF DEATH AND CARDIOVASCULAR EVENTS IN INITIALLY HEALTHY WOMEN WITH NEW ONSET ATRIAL FIBRILLATION

The cohort consisted of 34 721 health care professionals in the Woman’s Health Study (WHS) who agreed to prospective follow-up. They were age 49 to 59 (median 53) and free of AF and cardiovascular disease at baseline.

During a median follow-up of 15 years, 1011 (2.6%) women developed AF.

Incidence rate per 1000 person-years:

	AF	No AF
All-cause mortality	10.8	3.1
Cardiovascular mortality	4.3	0.57
Non-cardiovascular mortality	6.5	2.5

In the WHS cohort, at baseline, nearly half of the women who subsequently developed AF had hypertension, a third had hypercholesterolemia, and 9% were current smokers. (Were these women really “healthy” ?)

JAMA May 25, 2011; 305: 2080-87 Original investigation, first author David Conen, University Hospital, Basel, Switzerland

AF is an important risk factor. Even if it is the sole risk factor (which it rarely is) it requires treatment. Combined structural heart changes and classical risk factors for CVD, increase risk.

5-6 NEW EUROPEAN GUIDELINES ON ATRIAL FIBRILLATION

The European Society of Cardiology has published new guidelines for managing atrial fibrillation (AF). Key changes include the identification of more people at risk of embolic stroke; wider use of oral anticoagulants; a more pragmatic approach to rate control; and a lower threshold for catheter ablation. (CA)¹ The priorities in management of AF are stroke prevention, rate control, and rhythm control.

Stroke prevention: To incorporate new evidence of the role of oral anticoagulants, the simple and easily remembered CHAD scoring system² has been modified.

Recommended anticoagulant strategy by CHA2DS2-VAS score:

- 0 No treatment (This is preferred to aspirin)
- 1 Oral anticoagulant preferred to aspirin; dabigatran 110 mg may be an alternative to warfarin.

2 and above: Oral anticoagulant. Dabigatran 150 mg may be an alternative to warfarin.

If aspirin is used for score of 0-1, a dose of 75 mg is reasonable because the risk of bleeding is dose dependent. But there is no evidence of an incremental reduction in stroke risk.

Although aspirin is still considered a reasonable option in persons with a score 0-1, it is no longer the preferred option for most patients.

(Dabigatran, a direct thrombin inhibitor, has assumed a first place, replacing warfarin. The Europeans have had more experience with this drug than we have. Ed.)

Rate control vs. rhythm control: Rate control should be tried first, with rhythm control adopted for patients who remain symptomatic despite good rate control.

Rate control: The requirements for optimal rate control have been relaxed. One large trial compared lenient control aimed at a resting heart rate less than 110 vs. a resting rate of less than 80 with an increase of less than 110 with moderate exertion. New guidelines suggest lenient control initially and strict rate control in those who remain symptomatic. Beta-blockers remain the agent of choice for ventricular rate control. Non-dihydropyridine calcium blockers³ are second choice, adding digoxin if needed.

Rhythm control: Paroxysmal AF can be eliminated by catheter ablation (CA) in 80-90% of patients, although up to 40% will require a repeat procedure. A 5% rate of complications compares favorably with long term antiarrhythmic drug therapy (eg, dronedarone; amiodarone, which have major adverse effects). The threshold for CA should be low. Guidelines therefore suggest it is a reasonable first-line treatment of rhythm control instead of drug therapy, especially in patients with NYHA grade III and IV heart failure..

- 1 *Catheter ablation: A specially designed catheter is placed in a peripheral vein and directed to the right atrium. The atrial septum is pierced and the catheter enters the left atrium. The tip of the catheter is directed to the entries of the pulmonary veins into the left atrium. A heated end of the catheter destroys tissue around the entries, the source of the AF. (Obviously requires skill and experience.)*
- 2 *See the following full abstract for the updated Cha2DS2VAS. The score adds up to a maximum of 10 points. Very few patients with AF would have a score of 0. Almost all would receive anticoagulation.*
- 3 *There are about 20 dihydropyridine calcium blockers on the market. The suffix “dipine” denotes this class of drug (eg, amlodipine). Non-dihydropyridine calcium blockers are fewer in numbers (eg, verapamil; diltiazam). They produce a greater effect on the A-V node to slow ventricular rate in AF. Source: Wikipedia
See the full abstract.*

Facilitating A Good Death Is A Core Clinical Role For Doctors

5-7 LET'S TALK ABOUT DYING

Imagine a situation where most persons with a common condition do not have it diagnosed. Where opportunities are repeatedly missed to identify the problem and offer structured evidence-based care. Where people are too often denied a chance to influence their care in a planned proactive way.

What is the condition?

Dying.

Despite huge advances and successes in end-of-life care, we have not yet managed to transform care of dying. Many of us are afraid to discuss dying, leaving patients unprepared and unable to plan. We must do more talking about it if we are to give patients the best chance of a good death.

People with advanced progressive illness who are admitted to the hospital are often not identified for end-of-life care. Many who could benefit from palliative care never have that opportunity. Too many people still die in distress with uncontrolled symptoms, are inappropriately resuscitated, and have futile interventions. Changes are needed to ensure that those at the end of life do not continue to be admitted to hospitals.

Often, despite multiple conditions, repeated admissions, and poor prognosis, patients are never formally identified for end-of-life care. One family member said “ I wish the doctors had told me that my mother was dying”.

Most people do not discuss their preferences for end-of-life care with their families. This hampers planning of care. Few British people have discussed with their family the type of funeral they want, whether they have a will, where they would like to die, or the type of care and support they would want at the end of life. Importantly though, people do want to talk to health professionals about dying. More than three quarters of people think that it is part of health professional's job to talk to them about where they would like to be cared for when dying, and where they would like to die.

This is crucial because, although most would like to die at home, most die in the hospital. A staggering 20% of hospital beds are occupied by end-of-life care patients who do not need or want to be there.

Facilitating a good death is a core clinical role for doctors. They should try to decrease patient's fear of dying, and increase awareness about palliative care.

BMJ May 2, 2011; 342: 1153 Commentary by Mayur Lakhani, general practitioner and chairman of Dying Matters Coalition and the UK National Council for Palliative Care

This is the British experience. I believe the US experience is similar.

When and how to open the subject of dying may be difficult for many physicians. One suggestion I have read is simply ask "Are you at peace"? And go on from there.

Be mindful of ethnic differences. Some patients and families may be offended by the inference that death is near.

FULL ABSTRACTS MAY 2011

Immediate Treatment Is Urgent; Application Of Appropriate Treatment Is Often Low.

5-2 MEDICAL TREATMENT IN ACUTE AND LONG-TERM SECONDARY PREVENTION AFTER TRANSIENT ISCHEMIC ATTACK AND ISCHEMIC STROKE

The incidence of stroke is predicted to rise as the population ages. At present, incidence is greater than that of myocardial infarction. Stroke is extremely costly.

Although primary prevention is most important, secondary prevention is essential. Recurrent strokes are common, more severe than first strokes, and are more likely to cause dementia.

Progress has been made over the past decades in prevention of recurrence [Aspirin + dipyridamole 1977; warfarin 1983; carotid endarterectomy 1991; clopidogril 1996; BP reduction 2001; cholesterol reduction 2004]

Most persons with a history of transient ischemic attack (TIA), or an ischemic stroke (IS) now take several drugs long-term.

The combined effect of these different interventions is best determined by population-based studies. The 5-year risk of recurrent stroke in the UK declined from about 25% in 1981-86 to about 10% in 2002-10.

This review considers the evidence that led to this improvement in outcome. It is confined to the medical treatments that should be considered for most patients with TIA or IS. The approach to acute secondary treatment (the first 90 days after the event) will be considered separately from the long-term treatment. The evidence base differs.

ACUTE SECONDARY PREVENTION

A. Prognosis and triage:

Secondary prevention should be started urgently after a TIA or minor stroke.

Recent prospective studies have shown that stroke risk is much higher after a TIA and after a minor stroke (non-disabling) than previously thought. A meta-analysis reported that stroke risk was 3.1% at 2 days and 5.2% at 7 days. ABCD¹ system has been developed to help predict individual risk of stroke. It has good predictive power.

Patients with a low score (1.2.3.4) are more likely to sustain a second TIA than an IS

within 7 days; those with a high score (5,6,7) are more likely to develop a IS than a TIA. Brain and carotid imaging improve predictability.

B. Acute treatment after TIA or minor stroke:

Urgent treatment within 1 day improves prognosis. A delay in treatment of 20 days was associated with a 10% risk of stroke vs 2% when treatment was started at day one. Anti-platelets, anti-hypertensives, and statin drugs have been investigated—and anti-coagulants and carotid endarterectomy in special circumstances. The relative contribution of the treatments is not known.

Antiplatelets: Early administration of aspirin is beneficial. There is evidence that clopidogril + aspirin is more beneficial than aspirin alone, but at increased risk of bleeding.

Antihypertensive drugs: BP often rises shortly after a TIA or stroke. It tends to fall spontaneously during the first few days. Falling cerebral perfusion is less likely to be a concern after a TIA or minor stroke. Many clinicians start BP therapy immediately. This is not associated with a higher risk of stroke

Statin drugs: More evidence is needed for acute treatment. They are prescribed for long-term treatment.

LONG-TERM SECONDARY PREVENTION:

The evidence is more robust than for therapy of acute TIA or minor IS. But application of appropriate treatment is often low. Appropriate use of anti-platelet drugs and anti-coagulants depends on whether the underlying cause is cardio-embolic or presumed arterial origin.

A. Antiplatelet; anticoagulant

1) Arterial origin:

Aspirin is recommended for secondary prevention when the cause is arterial. The relative reduction in recurrence is small (~13%). Aspirin + dipyridamole vs aspirin alone is favored. Aspirin + clopidogril compared with clopidogril alone or with aspirin alone was associated with more bleeding, which nullifies any beneficial effects. There were more major bleeding events with combinations than with clopidogril alone.

Guidelines still recommend aspirin + dipyridamole (*Aggrenox*) or clopidogril as first-line treatment.

Vitamin K antagonists (eg. warfarin) are *not* recommended. Use is associated with increased intracranial hemorrhage.

2) Cerebral ischemia of cardiac origin:

About 20% of all TIA and ischemic stroke have a cardiac origin, most commonly with atrial fibrillation. (AF) There is much variation in risk of stroke in patients with AF. Variation can be assessed by risk scoring systems such as CHADS2 score².

In patients with a recent TIA or ischemic stroke of cardiac origin, vitamin K antagonists (eg, warfarin) are preferred. Maintain international normalized ratio (INR) at 2.5. This results in an absolute risk reduction of 8% annually in incidence of stroke, myocardial infarction, and systemic emboli. There are more hemorrhages, but the benefit outweighed the risk. Aspirin is of some value in patients who are ineligible for warfarin. Aspirin + clopidogril is *not* as effective as warfarin.

A trial of the direct thrombin inhibitor dabigatran 150 mg daily found fewer ischemic events with the same risk of hemorrhage as warfarin. A trial of a factor Xa inhibitor apixaban vs aspirin found a relative risk of primary outcome events of 0.45. Current guidelines still recommend warfarin as standard treatment in patients with AF. Long-term safety of the newer anticoagulants and their costs require further study.

B. Lipid modification

Evidence for benefit is weaker for ischemic stroke than for myocardial infarction. It is still important for both primary and secondary preventions of stroke. Statin drugs have proven effective in reducing all cardiovascular events, including a reduction in risk of stroke by 18%. Stroke death was reduced by 13%, but was significant only in secondary prevention.

One secondary prevention trial showed a 16% reduction in stroke recurrence and a 35% reduction in major coronary events in patients randomized to a highly effective statin (atorvastatin) vs placebo. (Cardio-embolic stroke was excluded.) Patients with carotid stenosis, diabetes, and chronic kidney disease benefited most. A reduction in

LDL-cholesterol to 70 mg/dL was associated with a 28% greater reduction compared with a reduction to 100.

Triglyceride reduction: A systematic review of all trials showed that reduction did not reduce risk.

HDL-cholesterol: Clinical trials and epidemiological studies have shown that increased HDL is associated with a reduction in risk of stroke even at low LDL concentrations. A meta-analysis of nicotinic acid in primary and secondary prevention showed a 30% reduction in progression of major cardiovascular events and reduced progression of carotid atherosclerosis. Use is limited by side-effects (flushing).

C. Antihypertensive drugs:

Hypertension (especially systolic) is the most important modifiable risk factor for stroke prevention, particularly in elderly people. It is an important risk factor for stroke in patients who have had a recent TIA or stroke. A meta-analysis showed that reductions in BP lowered risk of recurrent stroke by 26%. A larger reduction was associated with greater benefit. These results can probably be generalized, but many physicians are cautious about BP lowering in patients with severe carotid stenosis in whom aggressive lowering may increase risk of stroke.

Current guidelines recommend treatment with BP-lowering drugs in most patients with a history of TIA or stroke. Some studies favor a combination of an ACE inhibitor and a diuretic. Visit-to-visit variability in BP and episodic hypertension are powerful risk factors for stroke. Benefit of some antihypertensive drugs is attributed partly to reduced variability of BP. Reductions in mean systolic are similar with different classes of drugs, but calcium blockers and diuretics also reduce variability of BP. Beta-blockers increase variability.

The other important consequence of variability in BP in patients with previous TIA or stroke is the unreliability of single clinic measurements. Home BP monitoring often provides more reliable data.

D. Potential long-term benefit of aggressive multi-risk factor control:

Estimation of the combined effects of treatment of risk factors for secondary prevention is difficult. If one uses the observed treatment effect from randomized trials and assumes that the relative effects of each treatment are independent of the others,

treatment of all major risk factors is estimated to reduce risk of recurrent stroke by 80%.

Conclusion:

Secondary treatment with antiplatelet agents, antihypertensives, statins, and anticoagulation, and carotid endarterectomy as appropriate, should be initiated urgently after TIA or minor stroke. The risk of recurrent stroke is high.

For long-term secondary prevention, most guidelines recommend aspirin plus dipyridamole or clopidogril for cerebral ischemia of arterial origin. For cardiac origin, factor Xa inhibitors and thrombin inhibitors are challenging the current standard of vitamin K antagonists.

Lipid-lowering and antihypertensive treatments are warranted after both types of cerebral ischemia (arterial and cardiac).

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1 ABCD score for treatment immediately after a TIA or minor stroke: Age over 60 (1 point); Blood pressure over 140/90 (1 point); Clinical features—unilateral weakness (2), speech disturbance (1); Duration of TIA symptoms: > 60 minutes (2). 10-59 minutes (1); < 10 minutes (0) to predict the risk of stroke during the first several days after a TIA. The risk is 30% when the score is 6. This calls for especially urgent treatment. (Source: Wikipedia) 2.

2 CHADS score to assess long-term risk—see the following abstract

5-6 NEW EUROPEAN GUIDELINES ON ATRIAL FIBRILLATION

The European Society of Cardiology has published new guidelines for managing atrial fibrillation (AF). Key changes include the identification of more people at risk for AF; wider use of oral anticoagulants; a more pragmatic approach to rate control; and a lower threshold for catheter ablation. The priorities in management of AF are stroke prevention, rate control, and rhythm control.

Stroke prevention

To incorporate new evidence of the role of oral anticoagulants, the simple and easily remembered CHA₂DS₂-VAS scoring system has been modified.

CHA2DS2-VAS system

Risk	Score
Congestive heart failure	1
Hypertension	1
Age > 70	2
Diabetes	1
Stroke or TIA history	2
Vascular disease history	1
Age > 65	1
Sex (female)	1

Recommended anticoagulant strategy by CHA2DS2-VAS score:

0 No treatment (preferred to aspirin)

1 Oral anticoagulant preferred to aspirin; dabigatran 110 mg may be an alternative to warfarin.

2 and above: Oral anticoagulant. Dabigatran 150 mg may be an alternative to warfarin.

If aspirin is used for score of 0-1, the dose of aspirin of 75 mg is reasonable because the risk of bleeding is dose dependent. But there is no evidence of an incremental reduction in stroke risk. Although aspirin is still considered a reasonable option in persons with a score 0-1, it is no longer the preferred option for most patients.

Rate control vs. rhythm control

Trials comparing rate control with rhythm control (attempts to restore and maintain sinus rhythm) have shown similar outcomes with either strategy. These trials have used antiarrhythmic drugs and cardioversion for rhythm control, both of which have high failure rates. Maintenance of sinus rhythm is associated with better outcomes. Catheter ablation is more effective in maintaining sinus rhythm. Rate control should be tried first, with rhythm control adopted for patients who remain symptomatic despite good rate control.

Rate control

The requirements for optimal rate control have been relaxed. One large trial compared lenient control aimed at a resting heart rate less than 110 vs. a resting rate of less than 80 with an increase of

less than 110 with moderate exertion. There were no significant differences in outcomes. New guidelines suggest lenient control initially and strict rate control in those who remain symptomatic. If tachycardia cardiomyopathy is suspected, strict rate control is mandatory.

Beta-blockers remain the choice for rate control. Non-dihydropyridine calcium blockers are second. Adding digoxin next. Atrioventricular node ablation has a low complication rate. It is ideal for people committed to ventricular rate control who have rapid rates refractory to medical treatment.

Rhythm control

Paroxysmal AF can be eliminated by catheter ablation (CA) in 80-90% of patients, although up to 40% will require a repeat procedure. A 5% rate of complications compares favorably with long term antiarrhythmic drug therapy (eg, dronedarone; amiodarone, which have major adverse effects) The threshold for CA should be low.

One trial reported that CA was associated with better maintenance of sinus rhythm, improved symptom control, and better quality-of-life. Guidelines therefore suggest it is a reasonable first-line treatment of rhythm control instead of drug therapy, especially in patients with NYHA grade III and IV heart failure..

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London, UK

