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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 20-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 6 years can be accessed at www.practicalpointers.org

Richard T. James Jr. M.D.
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HIGHLIGHTS AND *EDITORIAL COMMENTS* JUNE 2008

Rivaroxaban Was Significantly More Effective, Just As Safe, And Much More Convenient

6-1 RIVAROXABAN VERSUS ENOXAPARIN FOR THROMBOPROPHYLAXIS AFTER HIP ARTHROPLASTY

The current options for extended thromboprophylaxis are limited. Low molecular weight heparins reduce events, but must be administered subcutaneously. They are cost-effective only if injections are used at home. Vitamin K antagonists (Warfarin) are difficult to manage. They have unpredictable pharmacological effects, numerous food and drug interactions, and require frequent monitoring.

Rivaroxaban (*Xarelto*; Bayer) is a direct inhibitor of activated factor X (Xa). This article describes a phase 3 trial with a suggested dose of 10 mg daily.

The trial randomized over 3100 persons who underwent hip arthroplasty to: 1) 10 mg oral rivaroxaban or 2) 40 mg enoxaparin (*Lovenox*; Sanofi-Aventis) injections daily for a mean of 35 days.

Primary efficacy outcome = composite of deep vein thrombosis (either symptomatic or detected by venography if the patient was asymptomatic), non-fatal pulmonary embolism, or death from any cause at 36 days.

Primary outcomes	Pro-protocol population	Modified intention-to treat
Rivaroxaban	0.8%	1.1%
Enoxaparin	3.4%	3.7%

Major venous thromboembolism occurred in 0.2% of the rivaroxaban group and 2.0% of the enoxaparin group.

Compared with enoxaparin, rivaroxaban was not associated with any significant increases in major bleeding or any other bleeding events

Conclusion: Once-daily 10 mg rivaroxaban was significantly more effective for extended thromboprophylaxis than once-daily 40 mg enoxaparin. The two drugs had similar safety profiles.

If this or similar drugs continue with the same effectiveness and safety for 2 or 3 years after approval and release to the general populations, I believe they will replace our current anticoagulant therapies.

They will be "blockbusting" drugs.

Only 18% Of Trials Included Patient-Important Outcomes As Primary Outcomes.

6-2 PATIENT-IMPORTANT OUTCOMES IN REGISTERED DIABETES TRIALS.

Trials measuring biochemical and surrogate markers may help researchers understand how, and to what extent, interventions could affect health. The value of these interventions remains unclear until trials test their effect on outcomes that are important to patients..

This review selected 436 RCTs which enrolled patient with type-2 diabetes.

Determined the outcomes measured, and their type (physiological outcomes, surrogate outcomes thought to reflect an increased risk for patient-important outcomes, and patient-important outcomes).

Patient –important outcomes: death and quality-of-life (stroke, myocardial infarction, amputation, loss of vision, end-stage renal disease). And other morbid events such as hypoglycemia, delayed wound healing, infection, visual disturbances, pain, and functional status.

Surrogate outcomes: intermediate endpoints that may indicate disease progression and increased risk for patient-important outcomes (eg, HbA1c, cholesterol, worsening renal function).

Physiological and laboratory outcomes: response to maneuvers without direct tangible effects
on patients (eg, insulin levels).

Primary outcomes of 436 trials:

Patient-important outcomes	18%
Physiological and laboratory outcomes	16%
Surrogate outcomes	61%

Conclusion: Only 18% of RCTs in diabetes measured outcomes important to patients as primary end points.

This is important to primary care, not only for diabetes, but also for many other diseases.

Surrogate outcomes are risk factors. Primary care clinicians depend on them.

Treatment of a surrogate outcome will depend on the primary care clinician's judgment of the benefit/harm-cost ratio of the intervention. And the individual patient's preference, after being fully informed.

Improving some surrogate outcomes will likely be associated with a high probability of reducing risk. Some will seem inconsequential. Clinicians should be able to provide the individual patient with some idea of the degree of possible benefits and harms of interventions. Life-style interventions take priority.

The individual patient's choice depends on many factors:

Cost.

Willingness to accept risk of some degree of harm from the intervention in order to obtain indefinite benefit in the future.

Ability and willingness to continue treatment long-term.

Willingness to accept ongoing monitoring of the effects of treatment.

"As Populations Age, The Burden Of CVD Attributable To BP Will Be Almost Entirely Related To Systolic Pressure".

6-3 SYSTOLIC PRESSURE IS ALL THAT MATTERS

Systolic hypertension is much more common then diastolic hypertension. Systolic BP contributes more to the huge burden attributable to hypertension than does diastolic.

There has undoubtedly been confusion about the relative merits of targeting systolic versus diastolic. This has led to poor recognition in the wider medical community of the importance of systolic BP.

Systolic rises; and diastolic falls after age 50, at a time when the risk of cardiovascular disease begins to rise.

The author proposes a simplified view of hypertension for most patients—ie, those over age 50—whereby the thresholds for the diagnosis and treatment of hypertension can be expressed in one dimension, systolic pressure. Distilling the risk imparted by high BP into a single number will greatly assist in both the communication of an important public health message to patients and policy makers, and in simplification of treatment targets.

As populations age, the burden of CVD attributable to BP will be almost entirely related to systolic pressure.

Trials of lowering BP in patients with isolated systolic hypertension have unequivocally confirmed the safety and impressive cardiovascular benefits of lowering systolic BP. But, systolic BP is more difficult to control than diastolic and invariably requires more drug therapy. If the focus of treatment was on systolic, there would hardly ever be a circumstance when diastolic was not controlled.

This approach focuses on individuals over age 50. Among individuals under age 40, as many as 40% with high BP have isolated diastolic hypertension. In patients under age 50, a continued emphasis of both systolic and diastolic remains appropriate. For these younger people, although diastolic should always be controlled, systolic should be the main target. This approach will produce adequate control of diastolic for all but a few patients.

I enjoyed this article. I believe the author makes a good point. Patients have difficulty understanding (and remembering) "systolic" and "diastolic". One number would be more meaningful, more easily remembered, and much more helpful to the patient in following effects of treatment.

Rate-Control Should Be Considered The Primary Approach

6-4 RHYTHM CONTROL VERSUS RATE CONTROL FOR ATRIAL FIBRILLATION AND HEART FAILURE

In patients with atrial fibrillation **(AF**), an excessive ventricular rate, a loss of atrial contraction and an irregular ventricular filling rate may have negative clinical consequences.

This multicenter, randomized trial of over 1300 patients (mean age = 67) compared the maintenance of sinus rhythm (rhythm–control) with control of ventricular rate (rate-control) in patients with AF who have HF. All had a left ventricular ejection of 35% or less, symptoms of HF, and a history of AF.

For rhythm-control, electric cardioversion was recommended within 6 weeks after randomization in patients who did not revert to sinus rhythm after antiarrhythmic drugs. Additional cardioversions were recommended for subsequent recurrences of AF. Amiodarone was the drug of choice.

For rate-control, adjusted doses of beta-blockers and digoxin were used to achieve the targeted rate, defined as less than 80 beats per minute during rest, and less than 110 beats per minute during a 6-minute walk.

Prevalence of AF at baseline in the rhythm-control group was 54%; at 3 weeks 33%; at 4 months 17%; at 4 years 27%. During follow-up, 58% of patients had at least one recurrence of AF.

During the study, 21% of the rhythm-control group crossed over to rate-control. 10% of the rate-control group crossed over to rhythm-control, most often due to worsening HF.

During the first 3 years of follow-up, the heart rate goal in the rate-control group was achieved in 88% of patients.

Results; The primary outcome, death from cardiovascular causes occurred in 27% of the rhythm-control group vs 25% in the rate-control. Secondary outcomes: overall survival, risk of stroke, and worsening HF were similar between groups. No significant differences favoring either strategy were noted in any of 10 prespecified subgroups.

The importance of this trial was that it compared strategies in patients with heart failure. This is consistent with trials that did not show any benefit of rhythm-control in patients without HF.

"The routine use of a rhythm-control strategy did not reduce the rate of death from cardiovascular causes, as compared with a rate-control strategy."

Conclusion: "Our results suggest that rate-control should be considered a primary approach for patients with atrial fibrillation and heart failure"

This was not a clean-cut trial. There were many cross-overs. Many subjects did not achieve and maintain the therapeutic goal. Many had to undergo repeated cardioversions.

I believe that, if we could achieve 100% conversion and maintenance of sinus rhythm easily and without toxicity, outcomes in rhythm-control would be more beneficial than in rate-control. As the authors state, AF has adverse effects on cardiac output. And is an independent predictor of death. Normal sinus rhythm is much more efficient. I believe we have not heard the last of attempts at cardioversion.

Meanwhile, rate-control is the preferred and easiest approach to patients with AF, with and without HF.

"At Least A Billion People Worldwide Are Vitamin D Deficient"

6-5 DEFICIENCY OF SUNLIGHT AND VITAMIN D

At least a billion people worldwide are vitamin D deficient due to inadequate sun exposure and lack of vitamin D in the diet.

Up to 25% of adults with vitamin D deficiency have symptoms of osteomalacia. Deficiency causes secondary hyperparathyroidism and increases destruction of the skeleton by precipitating or exacerbating osteopenia and osteoporosis. Unlike osteoporosis, which is painless, osteomalacia in adults can cause non-specific aches and pains in bones and muscles, and severe muscle weakness. It has been misdiagnosed as fibromyalgia, chronic fatigue syndrome and degenerative arthritis.

Vitamin D deficient persons have an increased risk of many cancers. Increasing the intake to 1000 IU per day reduces the risk of colon cancer. Deficiency is also linked to cardiovascular disease[2], autoimmune diseases, infectious diseases, and schizophrenia.

The only way to know a person's vitamin D status is to measure serum 25(OH)vitamin D concentrations. Concentrations of 75-150 nmol/L are recommended. 500 000 IU of D2 once a week for 8 weeks will correct deficiency. 1000 to 2000 IU daily will maintain sufficiency. Toxicity is very rare. Intoxication occurs when concentrations are greater than 375 nmol/L

"Vitamin D" perhaps should no longer be classified as a vitamin.

More reports are appearing about various adverse effects linked to deficiency

At present, I believe the article overstates the relationships. It may take a long time to clarify.

Meanwhile, primary care clinicians should be aware of the possibility that deficiency may be a cause of some symptoms, especially in elderly house-confined patients.

The ASH Now Is Calling For Individuals To Routinely Monitor Their BP At Home.

6-6 MANY PHYSICIAN PRACTICES FALL SHORT ON ACCURATE BLOOD PRESSURE MEASUREMENT

At the meeting of the American Society of Hypertension (**ASH**) in May 2008, experts stated, "Blood pressure reading does not seem to be done correctly in any medical clinic." "And yet, the single most important thing physicians do in their medical life is to take an accurate blood pressure measurement.".

"For patients, a proper assessment of blood pressure is more nuanced and time-consuming than they probably experience during most routine physician visits."

The article repeats the standard method of determining BP: (*See the full abstract. RTJ*)

A recent study reported that 14% of physicians and nurses failed to allow patients adequate time to rest. 24% preferred to take the BP with the patient lying on the table; 13% did not take arm level into account; 26% never, or hardly ever used an obese-cuff when necessary, often due to lack of an appropriate cuff.

Only 28% always or almost always took readings properly.

Home BP devices are gaining favor as a diagnostic tool, and to monitor response to therapy. The ASH now is calling for individuals to routinely monitor their BP at home.

All of us know the recommended procedure, I abstracted the article to refresh memory. My experience, when visiting my personal physician, correlates with the lack of proper BP recording. The nurse comes into the examining room, usually after I had tried to relax for 5 or more minutes. She then takes my BP while I am sitting. She takes it only once, and pronounces "Your blood pressure is X/Y"

If patients consistently used home BP readings, many primary care physicians would be less likely to worry about proper (ASH recommended) BP recording in the office. This would be a great time-saver.

Associated With A Reduced Risk Of Diabetes. Possibly A Protective Effect

6-7 ADHERENCE TO MEDITERRANEAN DIET AND RISK OF DEVELOPING DIABETES

Many studies have shown that the Mediterranean diet (**MD**) has a role in prevention of cardiovascular disease. Some suggest that the diet could protect against type-2 diabetes. (**DM-2**)

This prospective cohort study followed over 13 000 subjects in Spain. None had DM-2 at baseline. Periodic questionnaires assessed food frequency, risk factors, and medical conditions. Determined adherence to the MD using a score index divided into 3 categories (0-2; 3-6; and 7-9—9 being the highest adherence).

Follow-up = median of 4 years.

Identified 33 new-onset cases of DM-2 during follow-up (over 58 000 patient-years).

Patients with the highest MD score (> 6) had a higher level of leisure-time activity, but also had higher baseline prevalence of most risk factors (higher BMI, higher total energy intake, higher BP. a family history of DM-2, and were more likely to be former smokers).

After adjustment for age and sex, there was a significant inverse relationship between adherence to the MD and incidence of DM-2.

	Relative risk of DM-2
Low-score (0-2)	1.00 (reference)
Moderate score (3-6)	0.41
High score (7-9)	0.17

With score as a continuous variable, an increase of 2 points in the MD score was associated with a significant reduction in the risk of DM-2. This was despite the increase in baseline risk factors noted above, "suggesting that the diet might have a substantial potential for prevention".

Conclusion: Adherence to the Mediterranean diet was associated with a reduced risk of diabetes.

The study would be more convincing if it were continued longer, and if more subjects had developed DM-2.

The most interesting aspect was that those who were more adherent to the diet were less likely to develop DM-2, despite the fact that risk factors for DM-2 in this group were more prevalent. This suggests that the diet has a protective effect on development of DM-2 despite an increased prevalence of factors such as increased BMI and family history of DM-2.

Is the prevalence of DM-2 lower in Mediterranean populations?

Appears To Have A Reno-Protective Effect That Is Independent Of Its BP-Lowering Effect

6-8 ALISKIREN COMBINED WITH LOSARTAN IN TYPE-2 DIABETES AND NEPHROPATHY

Aliskiren directly inhibits production of renin by the kidney, thereby lowering production of angiotensin and aldosterone.

A reduction in proteinuria has been widely used as a surrogate end point for renoprotection.

This study evaluated the renoprotective effects of aliskirin by adding it to treatment with the maximum recommended dose (100 mg/d) of the angiotensin II blocker losartan (*Cozaar*; Merck), and with optimal antihypertension therapy in patients who had hypertension and type-2 diabetes with nephropathy.

Multinational, double-blind trial enrolled 599 patients (mean age 60). All had type-2 diabetes and nephropathy (defined as an early-morning urinary albumin/creatinine ratio of greater than 300 mg per gram). None had an estimated glomerular filtration rate of less than 30 mL per minute per 1.73 m^2 of body-surface area, serum potassium greater that 5.1 mmol/L, or major cardiovascular disease. Mean urinary albumin excretion rate = 500 ug/min. Baseline BP = 135/78

After a 3-month open-label run-in period during which all patients received 100 mg losartan daily, patients were randomized to:

1) Aliskiren 150 mg daily for 3 months followed by 300 mg daily for another 3 months + losartan. (300 mg is the optimum dose for treatment of hypertension..)
2) Placebo + losartan.
3) All patients continued to take other antihypertension drugs aimed at maximal recommended renoprotective dose (target BP < 130/80), except for other drugs blocking the renin-angiotensin-aldosterone system.

By 6 months treatment with aliskiren, the mean albumin/creatinine ratio was reduced by 20% as compared with placebo. A reduction of 50% or more was seen in 25% of aliskiren patients as compared with 13% in the placebo group. The overnight urinary albumin was reduced by a mean of 18% in the aliskiren group compared with placebo.

Adverse events: overall, no difference between groups. The rate of serious adverse events was similar—9%. Hyperkalemia occurred in 5% vs 5.7% of patients.

The benefit of aliskiren appeared to be independent of the small reduction in BP (2/1 mm Hg).

Conclusion: Aliskiren appears to have a reno-protective effect that is independent of its BP-lowering effect in patients with type-2 diabetes who are receiving maximally recommended reno-protective treatment and optimal antihypertension treatment.

Aliskiren (Tektura; Novartis) is approved by the FDA (2007) for treatment of hypertension. Starting dose is 150 mg/d. This is the first time I have abstracted an article abut it.

I believe aliskiren for renal protections is not a practical point for primary care at this time. I would not use the drug for treatment of hypertension until more time passes to evaluate general use.

6-9 RECENT CHANGES IN THE MANAGEMENT OF COMMUNITY ACQUIRED PNEUMONIA IN ADULTS

This review article considers:

How is community acquired pneumonia (**CAP**) diagnosed?

What organisms cause CAP?

How has etiology of CAP changed?

Community acquired methicillin resistant staphylococcus aureus. (MRSA)

Which antibiotics should be used for CAP treated in the community?

How quickly should we give antibiotics?

Length of treatment

Severity scores

Please consult the full abstract for useful clinical points.

ABSTRACTS JUNE2008

Rivaroxaban Was Significantly More Effective, Just As Safe, And Much More Convenient

6-1 RIVAROXABAN VERSUS ENOXAPARIN FOR THROMBOPROPHYLAXIS AFTER HIP ARTHROPLASTY

Prophylactic anticoagulation is standard practice after total hip arthroplasty. The minimum duration of therapy is 10 days. Extending the duration of therapy to 5 weeks reduces incidence of venous thromboembolism more effectively.

The current options for extended thromboprophylaxis are limited. Low molecular weight heparins reduce events, but must be administered subcutaneously. They are cost-effective only if injections are used at home. Vitamin K antagonists (Warfarin) are difficult to manage. They have unpredictable pharmacological effects, numerous food and drug interactions, and require frequent monitoring.

Rivaroxaban (*Xarelto*; Bayer) is a direct inhibitor of activated factor X (Xa). This article describes a phase 3 trial with a suggested dose of 10 mg daily.

Conclusion: Once-daily 10 mg rivaroxaban by mouth was significantly more effective for extended prophylaxis than once-a-day enoxaparin. The two drugs had similar safety profiles.

STUDY

1. Randomized, double-blind trial included over 3100 patients who underwent hip arthroplasty.
2. Randomized for a mean of 35 days. to: 1) 10 mg oral rivaroxaban daily beginning after surgery, or 2) 40 mg enoxaparin (*Lovenox*; Sanofi-Aventis; a low molecular weight heparin) injections daily beginning the evening before surgery,
3. Patients underwent mandatory bilateral venography on the last day.
4. Primary efficacy outcome = composite of deep vein thrombosis (either symptomatic or detected by venography if the patient was asymptomatic), non-fatal pulmonary embolism, or death from any cause at 36 days. Follow-up at one month after the last dose.

RESULTS

1. Primary efficacy outcome:

	Pro-protocol population	Modified intention-to treat
Rivaroxaban	0.8%	1.1%
Enoxaparin	3.4%	3.7%

(Rivaroxaban was non-inferior to enoxaparin.)

2. Major venous thromboembolism occurred in 0.2% of the rivaroxaban group and 2.0% of the enoxaparin group.

   (Rivaroxaban was superior to enoxaparin.)

3. Rates of symptomatic venous thromboembolism were similar 0.3% vs 0.5%

   Deaths—4 in each group. 2 deaths in the rivaroxaban group due to thromboembolism and 1 in the enoxaparin group.

   During the post-treatment follow-up, one patient in the rivaroxaban group developed symptomatic proximal deep vein thrombosis vs 3 in the enoxaparin group.

4. Safety:

	Rivaroxaban	Enoxaparin
Major bleeding	0.3%	0.1%
Combined clinically relevant + non-major bleeding	3.2%	2.5%
Hemorrhagic wound complications	1.5%	1.7%

   The number of patients receiving blood transfusions was similar—55% vs 56%. The median volume of blood transfusions was 568 mL vs 585 mL. (Typically patients undergoing hip arthroplasty receive 2 units of blood.)

   Elevations of plasma alanine (over 3 times normal) 2.0% vs 2.7%. All resolved at one month.

DISCUSSION

1. Rivaroxaban was significantly more effective for prevention of venous thromboembolic events.
2. Absolute risk reduction compared to enoxaparin = 2% for the primary efficacy outcome of deep-vein thrombosis, pulmonary embolism, or death from any cause –an absolute risk reduction = 1.7% for major venous thromboembolism.
3. Rivaroxaban was not associated with any significant increases in major bleeding or any other bleeding events.

CONCLUSION

Once-daily 10 mg rivaroxaban was significantly more effective for extended thromboprophylaxis than once-daily 40 mg enoxaparin. The two drugs had similar safety profiles.

NEJM June 26, 2008; 358: 2765-75 Original investigation by the Regulation of Coagulating in Orthopedic Surgery to Prevent Deep Vein Thrombosis (RECORD1) Study Group, first author Bengt I Eriksson, Sahlgrenska University Hospital, Gothenburg, Sweden.

A similar trial "Rivaroxaban versus Enoxaparin for Thromboprophylaxis after Total Knee Angioplasty" appeared in this issue of NEJM. Results again favored rivaroxaban.

An editorial in this issue of NEJM, first author Jens Lohrmann, University of Freiburg, Germany comments: "Gone are the days of nonselective anticoagulants with unfavorable pharmacokinetics and pharmacodynamics, archaic and highly vulnerable manufacturing processes, and predictably unpredictable target-effects." At present thromboprophylaxis after orthopedic surgery, despite its efficacy and wide recommendation, is offered to less than 60% of patients.

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Only 18% Of Trials Included Patient-Important Outcomes As Primary Outcomes.

6-2 PATIENT-IMPORTANT OUTCOMES IN REGISTERED DIABETES TRIALS.

Trials measuring biochemical and surrogate markers may help researchers understand how, and to what extent, interventions could affect health. The value of these interventions remains unclear until trials test their effect on outcomes that are important to patients.

Patient-important outcomes include quality-of-life (morbidity, pain, function) and death.

Trials often mention only physiological and laboratory outcomes.

A recent consensus statement on how to choose antidiabetes agents to treat patients with type-2 diabetes (**DM-2**) was based on recommendations of trials that measured the effect of these agents on physiological or surrogate markers.

Concerns about the safety and efficacy of DM-2 interventions persist because their effects on patient-important outcomes may not be measured.

This systematic review determined the extent to which ongoing and future randomized, controlled trials (**RCTs**) ascertain patient-important outcomes.

Conclusion: Only 18% of trials included patient-important outcomes as primary outcomes.

STUDY

1. Selected 436 RCTs which enrolled patients with DM-2.
2. Determined the outcomes measured, and their type (physiological outcomes, surrogate

outcomes thought to reflect an increased risk for patient-important outcomes, and patient-important outcomes).

3. Patient –important outcomes: included death and quality-of-life (stroke, myocardial infarction, amputation, loss of vision, end-stage renal disease). And other morbid events such as hypoglycemia, delayed wound healing, infection, visual disturbances, pain, and functional status.
4. Surrogate outcomes: intermediate endpoints that may indicate disease progression and increased risk for patient-important outcomes (eg, HbA1c, cholesterol, worsening renal function).
5. Physiological and laboratory outcomes: response to maneuvers without direct tangible effects on patients (eg, insulin levels).

RESULTS

1. The majority of registered trials were phase 3 or 4, parallel-design RCTs involving adults with DM-2.
2. Primary outcomes of 436 trials:

Patient-important outcomes	18%
Physiological and laboratory outcomes	16%
Surrogate outcomes	61%

DISCUSSION

1. Only a minority of registered RCTs in DM-2 measured outcomes of importance to patients as primary end points.
2. This reflects the need for larger and longer trials to assess the impact of interventions on outcome. Surrogate outcomes are preferred by research and funding agencies in order to obtain results faster, with fewer patients at lower costs.
3. A major downside of such trials is that the results cannot be used with confidence in patient care because they do not provide information about benefits patients would consider important.
4. Surrogates such as HbA1c are commonly used in DM-2 trials, but are problematic as guides for patient care. The validity of HbA1c as a surrogate for cardiovascular complications in patients with DM-2 is highly questionable.
5. One approach to increasing patient-important outcomes in RCTs as primary endpoints is to conduct very large trials that will produce definitive evidence. In this era of meta-analyses, it is important for trialists to carefully measure patient-important outcomes, even as secondary outcomes, and make their reports subject to pooling. Without pooling, individual DM-2 trials will largely fail in providing information about the effect of interventions on patient-important outcomes.

6. The investigators have noted similar reliance on surrogates in conditions other than diabetes.
7. “We believe the time has come for a broad consensus on a standard set of important outcomes for patients in diabetes trials.”

CONCLUSION

Only 18% of RCTs in diabetes measured outcomes important to patients as primary end points.

JAMA June 4, 2008; 299: 25 43-49 Original investigation, first author Gunjan Y Gandhi, College of Medicine, Mayo Clinic, Rochester, Minn.

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As Populations Age, The Burden Of CVD Attributable To BP Will Be Almost Entirely Related To Systolic Pressure.

6-3 SYSTOLIC PRESSURE IS ALL THAT MATTERS

Systolic hypertension is much more common then diastolic hypertension. Systolic BP contributes more to the huge burden attributable to hypertension than does diastolic. In the past, interest was focused on diastolic pressure.

There has undoubtedly been confusion about the relative merits of targeting systolic versus diastolic. This has led to poor recognition in the wider medical community of the importance of systolic BP.

The author proposes a simplified view of hypertension for most patients—ie, those over age 50—whereby the thresholds for the diagnosis and treatment of hypertension can be expressed in one dimension, systolic pressure. Distilling the risk imparted by high BP into a single number will greatly assist in both the communication of an important public health message to patients and policy makers, and in simplification of treatment targets.

There is a clear association between raised systolic or diastolic BP and risk of cardiovascular disease. What has not been emphasized is the changing burden of disease attributable to systolic pressure versus that attributable to diastolic. BP profiles change with increasing age. Systolic rises; diastolic falls after age 50, at a time when the risk of cardiovascular disease begins to rise.

There is an increased prevalence of high systolic over age 50, and an almost total disappearance of high diastolic. Since more than 75% of people with high BP are over age 50, the burden of disease is mainly due to systolic pressure. As populations age, the burden of CVD attributable to BP will be almost entirely related to systolic pressure. “The use of diastolic pressure for diagnosis and risk stratification in our aging population has become illogical.”

In younger people, higher systolic and diastolic pressures are caused mainly by an increase in peripheral vascular resistance due to narrowing of resistance arteries and arterioles. As age advances, structural damage and disease of the larger conduit arteries becomes a more important determinant of BP. Large artery changes result in stiffening and loss of vascular compliance, thereby reducing the buffering capacity of the arterial system. This causes a rise in systolic and a fall in diastolic, and widening of the pulse pressure. Increased pulse pressure (difference between systolic and diastolic) indicates large artery disease and is associated with increased risk of CVD. Assessment of systolic pressure is sufficient to capture this component of risk since there is hardly ever a situation in which pulse pressure is increased in the context of a normal systolic.

Trials of lowering BP in patients with isolated systolic hypertension have unequivocally confirmed the safety and impressive cardiovascular benefits of lowering systolic BP. But, systolic BP is more difficult to control than diastolic and invariably requires more drug therapy. If the focus of treatment was on systolic, there would hardly ever be a circumstance when diastolic was not controlled.

Redirecting our clinical focus *exclusively* toward systolic in people over age 50 is now appropriate for 4 reasons:

1) Systolic BP is more easily and accurately measured. It is a better predictor of risk. Indeed, diastolic is often normal or low in high risk patients.
2) Communication of the concept of hypertension as two different numbers has left many patients confused abut the relative importance of systolic and diastolic. Focusing on a single number would make communication easier.
3) Many physicians have been confused by conflicting messages about diastolic and systolic. Many still use diastolic to guide their clinical management.
4) Focusing the public health messaging on a single number for patients over age 50 has the potential to dramatically improve the treatment and control of systolic BP and reduce cardiovascular morbidity and mortality.

This approach focuses on individuals over age 50. Among individuals under age 40, as many as 40% with high BP have isolated diastolic hypertension. In patients under age 50, a continued emphasis of both systolic and diastolic remains appropriate. For these younger people, although diastolic should always be controlled, systolic should always be the main target. This approach will produce adequate control of diastolic for all but a few patients.

A renewed focus on systolic pressure will simplify the message for practitioners and for patients, will improve awareness and understanding of treatment objectives, and will ultimately lead to more effective treatment.

Lancet June 28, 2008; 371: 2219-21 "Viewpoint", commentary, first author Bryan Williams, University of Leicester, UK

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Rate-Control Should Be Considered The Primary Approach

6-4 RHYTHM CONTROL VERSUS RATE CONTROL FOR ATRIAL FIBRILLATION AND HEART FAILURE

It is a common practice to restore and maintain sinus rhythm in patients with atrial fibrillation **(AF**) and heart failure (**HF**). This approach is based on data indicating that AF is an independent predictor of death in patients with HF, and suggesting that suppression of AF may favorably affect outcome. In patients with AF, an excessive ventricular rate, a loss of atrial contraction and an irregular ventricular filling rate may have negative clinical consequences.

Restoration and maintenance of sinus rhythm with electric cardioversion and antiarrhythmic drugs are often attempted.

AF can lead to HF, and HF can lead to AF. AF is present in 10 to 50% of patients with HF.

This trial compared the induction and maintenance of sinus rhythm (rhythm control) vs control of the ventricular rate (rate-control) in patients with AF who have HF.

Conclusion: Rhythm-control did not reduce rate of death from cardiovascular causes, as compared with a rate-control strategy.

STUDY

1. Multicenter, randomized trial of over 1300 patients (mean age = 67) compared the maintenance of sinus rhythm with control of ventricular rate.
2. All had a left ventricular ejection of 35% or less, symptoms of HF, and a history of AF. About 1/3 had class III or IV HF at baseline; 2/3 during the previous 6 months. About 2/3 had persistent AF; 1/3 paroxysmal AF. One third had previous cardioversion. None had persistent AF for more than 12 months.
3. Anticoagulation was recommended for all.
4. Rhythm control:

   Electric cardioversion was recommended within 6 weeks after randomization in patients who did not revert to sinus rhythm after antiarrhythmic drugs. Additional cardioversions were recommended for subsequent recurrences of AF.

Amiodarone was the drug of choice.

4. Rate control:

   Adjusted doses of beta-blockers and digoxin were used to achieve the targeted rate, defined as less than 80 beats per minute during rest, and less than 110 beats per minute during a 6-minute walk.

5. Therapies for HF:

   Included an ACE-inhibitor or an angiotensin receptor blocker for all patients. Maximum doses of beta-blockers were recommended for patients in both groups.

6. Primary outcome = time to death from cardiovascular causes. Follow-up = a mean of 37 months.

RESULTS

1. During the study, 21% of the rhythm-control group crossed over to rate-control; 10% of the rate-control group crossed over to rhythm-control, most often due to worsening HF.
2. Rhythm control:

   Prevalence of AF at baseline 54%; at 3 weeks 33%; at 4 months 17%; at 4 years 27%.

   During follow-up, 58% of patients had at least one recurrence of AF.

3. Rate control:

   Prevalence of AF ranged from 59% to 70% during follow-up.

   At baseline, the target rate was present in 72% of patients on the 6-minute walk test. During the first 3 years of follow-up, the heart rate goal was achieved in 88% of patients.

4. Primary outcome: Death from cardiovascular causes (80% of all deaths)—rhythm-control 27%; rate-control 25%.
5. Secondary outcomes: overall survival; risks of stroke; worsening HF were similar between groups. No significant differences favoring either strategy were noted in any of 10 prespecified subgroups.
6. The proportions of patients requiring hospitalization was higher in the rhythm-control group—

   More in the rhythm-control group underwent electric cardioversion—59% vs 9%.

DISCUSSION

1. The importance of this trial was that it compared strategies in patients with heart failure. This is consistent with trials that did not show any benefit of rhythm-control in patients without HF.
2. “The routine use of a rhythm-control strategy did not reduce the rate of death from cardiovascular causes, as compared with a rate-control strategy.”
3. There were no significant differences in important secondary outcomes.

4. Use of implantable defibrillators was low in this trial. About 1/3 of deaths were presumed to be associated with arrhythmia. Wider use of defibrillators might have decreased mortality.
5. Patients in the rhythm-control group were more likely to be hospitalized, in part because of the need for repeat cardioversion, and adjustments in antiarrhythmic therapy.
6. Most patients in the rhythm-control groups were free of AF at repeated assessments. Not all were in sinus rhythm at all times. Some patients in the rate-control group were in sinus rhythm during follow-up.
7. The potential benefit of sinus-rhythm maintenance with respect to mortality may have been neutralized by harmful effects of currently available antiarrhythmic therapies.

CONCLUSION

1. "Our results suggest that rate-control should be considered a primary approach for patients with atrial fibrillation and heart failure"

NEJM June 19, 2008; 358; 2667-77 Original investigation by the Atrial Fibrillation and Congestive Heart Failure Investigators, first author Denis Roy, Montreal Heart Institute, Montréal, Canada.

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"At Least A Billion People Worldwide Are Vitamin D Deficient"

6-5 DEFICIENCY OF SUNLIGHT AND VITAMIN D

At the beginning of the early 20th century, 80% of children living in Western industrial cities had rickets. Now rickets is extremely rare because of the understanding that sunlight is a major source of vitamin D, and fortification of foods.

Still, at least a billion people worldwide are vitamin D deficient due to inadequate sun exposure and lack of vitamin D in the diet.

Up to 25% of adults with vitamin D deficiency have symptoms of osteomalacia. Deficiency causes secondary hyperparathyroidism and increases destruction of the skeleton by precipitating or exacerbating osteopenia and osteoporosis. Unlike osteoporosis, which is painless, osteomalacia in adults can cause non-specific aches and pains in bones and muscles, and severe muscle weakness.

An accompanying article in this issue of BMJ[1] presents two cases of severe vitamin D deficiency which were misdiagnosed as fibromyalgia, chronic fatigue syndrome, and degenerative arthritis.

Proximal muscle weakness is a common feature of deficiency, It can be misdiagnosed as multiple sclerosis, or amyotrophic lateral sclerosis.

People who live at higher latitudes lack exposure to the sun [25(OH)vitamin D concentrations vary greatly with the season] and have increased risk of vitamin D deficiency.

Vitamin D deficient persons have an increased risk of many cancers. Increasing the intake to 1000 IU per day reduces the risk of colon cancer. Deficiency is also linked to cardiovascular disease[2], autoimmune diseases, infectious diseases, and schizophrenia.

Vitamin D may have many health benefits because all tissues have vitamin D receptors. It controls (directly or indirectly) more than 200 genes that regulate calcium and bone metabolism, modulate innate immunity, control cell growth and maturation, regulate the production of insulin and renin, induce apoptosis, and inhibit angiogenesis.

The only way to know a person's vitamin D status is to measure serum 25(OH)vitamin D concentrations. Concentrations of 75-150 nmol/L are recommended. 500 000 IU of D2 once a week for 8 weeks will correct deficiency. 1000 to 2000 IU daily will maintain sufficiency. Toxicity is very rare. Intoxication occurs when concentrations are greater than 375 nmol/L.

Public heath campaigns that emphasize the insidious consequences of deficiency on health are needed. Aggressive fortification of foods should be recommended.

BMJ June 14, 2008; 336: 1318-19 Editorial by Michael F Holick, Boston University Medical Center, Boston Mass.

1 "Unrecognized Severe Vitamin D Deficiency" BMJ June 14, 2008; 336: 1371-74, first author John L Sievenpiper, Royal Victoria Infirmary, Newcastle Upon Tyne, UK

2 "25-hydroxyvitamin D and Risk of Myocardial Infarction in Men: A Prospective Study" in the June 9 2008 issue of Archives Internal Medicine reports that low levels of 25(OH)D are associated with higher risk of myocardial infarction in a graded manner, even after controlling for other risk factors.

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The ASH Now Is Calling For Individuals To Routinely Monitor Their BP At Home.

6-6 MANY PHYSICIAN PRACTICES FALL SHORT ON ACCURATE BLOOD PRESSURE MEASUREMENT

At the meeting of the American Society of Hypertension (**ASH**) in May 2008, experts stated "Blood pressure reading does not seem to be done correctly in any medical clinic." "And yet, the single most important thing physicians do in their medical life is to take an accurate blood pressure measurement".

"For patients, a proper assessment of blood pressure is more nuanced and time-consuming than they probably experience during most routine physician visits."

The article repeats the standard method of determining BP:

1) The patient should sit quietly in a straight-backed chair to provide back support.
2) Feet should rest on the floor. Allow to rest at least 5 minutes.
3) The arm should rest on a table so that the cuff is the same height as the heart.
4) The bladder of the cuff should encircle at least 80% of the arm.
5) Readings should be taken in both arms with subsequent measurements taken in the limb providing the higher BP. The patient should not talk.

(*No mention of how many times to take BP to calculate the average. Some authorities advocate 3 readings, ignoring the 1st and averaging the 2nd and 3rd. RTJ)*

A recent study reported that 14% of physicians and nurses failed to allow patients adequate time to rest. 24% preferred to take the BP with the patient lying on the table; 13% did not take arm level into account; 26% never, or hardly ever used an obese-cuff when necessary, often due to lack of an appropriate cuff.

Only 28% always or almost always took readings properly.

Many physicians had never heard of these ASH guidelines, and only 8% had read them.

One major problem is lack of nurse and physician time. Another is that staff is not properly trained to take BP correctly.

Home BP devices are gaining favor as a diagnostic tool, and to monitor response to therapy. The ASH now is calling for individuals to routinely monitor their BP at home. (The machines need calibration. Many machines tend to underestimate BP.) Some authorities ask patients to take paired home BP readings morning and evening for a week. This supplies a running average. Then repeat the process in a month or two.

Home readings may be especially useful for older patients, who are more likely to have BP variability and the white-coat effect.

The home BP target should be less than 135/85; or 130/85 or less for those at high risk of cardiovascular disease. The home targets are less than those recommended for in-office readings because home readings are averages, and include readings taken at night, when BP tends to be lower.

JAMA June 25, 2008; 299: 2842-43 “Medical News and Perspective” by Mike Mitka, of the JAMA staff.

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Associated With A Reduced Risk Of Diabetes. Possibly A Protective Effect

6-7 ADHERENCE TO MEDITERRANEAN DIET AND RISK OF DEVELOPING DIABETES

Many studies have shown that the Mediterranean diet (**MD**) has a role in prevention of cardiovascular disease. Some suggest that the diet could protect against type-2 diabetes. (**DM-2**)

The protective characteristics of the diet include a high intake of plant-based foods (fruits, vegetables, and legumes), fiber and vegetable fat, moderate intake of alcohol, abundant use of virgin olive oil (rich in monounsaturated fat) , and a high intake of fish, and a low intake of meat and trans fat.

Diets high in monounsaturated fatty acids improve lipid profiles, insulin sensitivity, and glycemic control in people with DM-2.

This study evaluated the association between adherence to the MD and incidence of DM-2.

Conclusion: Adherence to the MD was associated with a reduced risk of developing DM-2.

STUDY

1. Prospective cohort study followed over 13 000 subjects in Spain. None had DM-2 at baseline.
2. Periodic questionnaires assessed food frequency, risk factors, and medical conditions.
3. Determined adherence to the MD using a score index divided into 3 categories (0-2; 3-6; and 7-9 (9 being the highest adherence).
4. Also estimated daily physical activity (MET score) by a questionnaire.
5. Follow-up = median of 4 years.

RESULTS

1. Identified 33 new-onset cases of DM-2 during follow-up (over 58 000 patient-years).
2. Patients with the highest MD score (> 6) had a higher level of leisure-time activity, but also had higher baseline prevalence of most risk factors (higher BMI, higher total energy intake, higher BP, a family history of DM-2, and were more likely to be former smokers).
3. After adjustment for age and sex, there was a significant inverse relationship between adherence to the MD and incidence of DM-2.

	Relative risk of DM-2
Low-score (0-2)	1.00 (reference)
Moderate score (3-6)	0.41
High score (7-9)	0.17

4. With score as a continuous variable, an increase of 2 points in the MD score was associated with

a significant reduction in the risk of DM-2. This was despite the increase in baseline risk factors noted above, “suggesting that the diet might have a substantial potential for prevention”.

DISCUSSION

1. “High adherence to the diet (score > 6) was associated with an 83% relative reduction in the risk of developing diabetes.”
2. A two-point increase in the score resulted in a 35% relative reduction in risk of developing DM-2.
3. The older, higher risk persons who were most adherent to the MD had a low risk of developing DM-2. This suggests a protective effect of the diet.

CONCLUSION

Adherence to the Mediterranean diet was associated with a reduced risk of diabetes.

BMJ June 14, 2008; 336: 1348-51 Original investigation, first author M A Martinez-Gonzalez, University of Navarra, Pamplona, Spain

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Appears To Have A Reno-Protective Effect That Is Independent Of Its BP-Lowering Effect

6-8 ALISKIREN COMBINED WITH LOSARTAN IN TYPE-2 DIABETES AND NEPHROPATHY

Aliskiren directly inhibits production of renin by the kidney, thereby lowering production of angiotensin and aldosterone.

Nephropathy is the leading cause of end-stage renal disease. The renin-angiotensin-aldosterone system plays an important role.

Persistent proteinuria is the hallmark of diabetic nephropathy, which is also characterized by a progressive rise in BP, a declining glomerular filtration rate, and high risk for cardiovascular events. The degree of proteinuria is closely associated with renal and cardiovascular events.

Reducing proteinuria is associated with slowing the decline in the glomerular filtration rate and progression of end-stage renal disease. It is also associated with improved cardiovascular outcomes in patients with diabetic nephropathy and hypertension.

A reduction in proteinuria has been widely used as a surrogate end point for renoprotection.

This study evaluated the renoprotective effects of aliskirin by adding it to treatment with the maximum recommended dose (100 mg/d) of the angiotensin II blocker losartan (*Cozaar*; Merck), and with optimal antihypertension therapy in patients who had hypertension and type-2 diabetes with nephropathy.

Conclusion: Aliskiren may have renoprotective effects that are independent of BP-lowering.

STUDY

1. Multinational, double-blind trial enrolled 599 patients (mean age 60). All had type-2 diabetes and nephropathy (defined as an early-morning urinary albumin/creatinine ratio of greater than 300 mg per gram). None had an estimated glomerular filtration rate of less than 30 mL per minute per 1.73 m^2 of body-surface area, serum potassium greater that 5.1 mmol/L, or major cardiovascular disease. Mean urinary albumin excretion rate = 500 ug/min. Baseline BP = 135/78
2. After a 3-month open-label run-in period during which all patients received 100 mg losartan daily, patients were randomized to:
    1) Aliskiren 150 mg daily for 3 months followed by 300 mg daily for another 3 months + losartan. (300 mg is the optimum dose for reduction in BP.)
    2) Placebo + losartan.
    3) All patients continued to take other antihypertension drugs aimed at maximal recommended renoprotective dose (target BP < 130/80), except for other drugs blocking the renin-angiotensin-aldosterone system.
4. Patients were examined periodically before and after randomization.
5. Primary efficacy measure = percentage reduction in early-morning albumin/creatinine ratio from baseline to end of study.

RESULTS

1. By 6 months treatment with aliskiren, the mean albumin/creatinine ratio was reduced by 20% as compared with placebo. A reduction of 50% or more was seen in 25% of aliskiren patients as compared with 13% in the placebo group.
2. The overnight urinary albumin was reduced by a mean of 18% in the aliskiren group compared with placebo.
3. BP changed little—2/1 mmHg lower in the aliskiren group.
4. The mean glomerular filtration rate declined in both groups, less in the aliskiren group.
5. Adverse events: overall, no difference between groups. The rate of serious adverse events was

similar—9%. Hyperkalemia occurred in 5% vs 5.7% of patients.

DISCUSSION

1. Treatment with 300 mg aliskiren daily reduced the albumin/creatinine ratio in patients with hypertension, type-2 diabetes, and proteinuria who were receiving the recommended maximal renoprotective treatment with losartan and optimal antihypertension treatment. Total urinary albumin excretion fell by about 12% in the aliskiren group vs increasing in the placebo group by about 3%.
2. The benefit of aliskiren appeared to be independent of the small reduction in BP.
3. Most studies report that renal disease progresses in many patients despite treatment with ACE inhibitors or angiotensin II receptor blockers. More complete blockade may lead to better outcomes.

CONCLUSION

Aliskiren appears to have a reno-protective effect that is independent of its BP-lowering effect in patients with type-2 diabetes who are receiving maximally recommended reno-protective treatment and optimal antihypertension treatment.

NEJM June 5, 2008; 358: 2433-46 Original investigation by the Aliskiren in the Evaluation of Proteinuria in Diabetes (AVOID) Study Investigators, fist author Hans-Henrik Parving, Rigshospitalet, Copenhagen, Denmark

Supported by Novartis Pharma.

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6-9 RECENT CHANGES IN THE MANAGEMENT OF COMMUNITY ACQUIRED PNEUMONIA IN ADULTS

How is community acquired pneumonia (**CAP**) diagnosed?

A review of studies that used clinical definitions based on symptoms and signs found that these alternative definitions were inferior to radiography in detecting CAP.

What organisms cause CAP?

Microbiological causes can be made in up to 75% of cases in the hospital. In real life practice, the rate of microbiological diagnosis is low—around 10-20%.

World-wide, the most common causative organism worldwide is still Streptococcus pneumoniae. Incidence of less common organisms is variable, depending on geography, heathcare setting, and availability of diagnostic tests.

The most common organisms in order of prevalence:

Strep pneumoniae

Mycoplasma pneumoniae

Hemophilus influenzae

Chlamydia pneumoniae

Respiratory viruses

(Legionella species are added in hospitalized patients)

Atypical pneumonia refers to pneumonia caused by organisms such as Mycoplasma, Chlamydia, and Legionella. One study reported a prevalence of 22% in cases of CAP in which an organism was identified.

How has etiology of CAP changed?

World-wide there have been no major changes.

The heptavalent pneumococcus vaccine, now given commonly to young children, was associated with a decrease in invasive pneumococcal disease in unvaccinated children as well as in vaccinated children and adults. This suggested that children were the major reservoir for the disease, and that herd immunity may be important.

The prevalence of non-vaccine serotypes then began to rise (disease replacement), particularly for strains that were not sensitive to penicillin.

The increase in strains that were not covered by the vaccine, and their increased antibiotic resistance, may mean that the heptavalent vaccine is little more than a holding mechanism in our fight against this deadly infection.

In the UK, the prevalence of pneumococci which are not sensitive to penicillin is about 3%.

Community acquired methicillin resistant staphylococcus aureus. (MRSA)

Is a rare cause of pneumonia. It is deadly. It causes severe necrotizing pneumonia.

It is associated with influenza.

Vancomycin or linezolid (*Zyvox*; Pharmacia Upjohn) are preferred treatment.

Which antibiotics should be used for CAP treated in the community?

Because the causative organism is not often determined, empirical treatment is begun.

Guidelines differ between the UK and USA.

Preferred treatment

British Thoracic Society (BTS)	Preferred	Alternative
	Oral amoxicillin	Oral erythromycin or clarithromycin
American Thoracic Society (ATS)		
No comorbidities	Oral azithromycin, clarithromycin, or erythromycin	Oral doxycycline
Comorbidities present	Oral moxifloxacin, gemifloxacin, or levofloxacin	Oral amoxicillin plus a macrolide

A recent world wide meta-analysis of patients with non-severe CAP found no evidence for the empirical use of antibiotics active against atypical pathogens and recommended sole use of beta-lactam antibiotics in non-severe pneumonia.

However, use of antibiotics effective against atypical pathogens in severe CAP treated in the hospital is advisable.

How quickly should we give antibiotics?

It seems logical to give antibiotics early. Recent guidelines have recommended this.

In 2004, a review reported that rapid delivery of antibiotics reduced mortality and length of hospital stay in patients given their first dose within 4 hours.

A recent study reported that, for patients given their first dose within 4 hours of admission led to many of these patients being incorrectly diagnosed as having pneumonia. This led to greater use of unnecessary antibiotics and possible adverse effects and development of resistance.

The ATS still advocates giving the first dose in the emergency department.

This controversy is not settled.

Length of treatment

For uncomplicated CAP treated in the community, the ATS suggest a minimum of 5 days; the BTS at least 7 days, and 10 days for patients with severe disease.

Severity scores

The CURB-65 severity score

C Confusion

U Urea > 7.0 mmol/L

R Respiratory rate 30 or more / min

B Blood pressure 90/60 or less

65 Age 65 or over.

0-1 probably suitable for outpatient care; 2 consider hospital; 3,4,5,6 manage in hospital

The CRB-65 score

Excludes urea since it not often done. Studies have reported that CRB-65 is equal to CURB-65 in predicting death.

The scores do not take into account comorbidities or the extent of the pneumonia.

A major question, that has yet to be answered, is whether stratifying patients with CAP into severity classes actually improves outcomes.

BMJ June 21, 2008; 336: 33 "Clinical Review", first author Hannah J Durrington, University of Cambridge, Addenbrooke's Hospital, Cambridge, UK

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