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ANTIBIOTIC TREATMENT OF COMMUNITY-ACQUIRED PNEUMONIA [9-1]

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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.

Editor/Publisher.

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HIGHLIGHTS AND EDITORIAL COMMENTS SEPTEMBER 2009

Cover Both Typical And Atypical Organisms

9-1 GUIDELINE-RECOMMENDED ANTIBIOTICS IN COMMUNITY-ACQUIRED PNEUMONIA: Not Perfect, but Good

Patients hospitalized with community-acquired pneumonia (CAP) can be infected with both typical and atypical (eg, *Legionella*) bacteria. Clinical features at presentation are not specific enough to consistently predict the causative agent. Absent unique epidemiological characteristics, the overwhelming majority of patients must be treated empirically.

Guidelines have been published recommending specific empirical antibiotic regimens. (*See the full abstract*)

A growing body of evidence supports the use of empirical regimens to target both typical and atypical organisms.

Three retrospective cohort studies in different settings reported that patients who received guideline-concordant antibiotics had decreased in-hospital and 30-day mortality. Two large Medicare studies of elderly patients admitted with CAP also reported a lower 30-day mortality in patient treated with antibiotics compliant with guidelines. After attempts were made to control for potential confounders, benefits were significant. The absolute risk reduction averaged 5%. (NNT = 20).

Two articles in this issue of *Archives* add to the literature regarding appropriate empirical use of antibiotics for CAP. They support the current guidelines. (*See the full abstract*)

For clinicians, the 2 studies add to the growing body of robust evidence supporting guideline-recommended antibiotic regimens. No research has documented clear negative consequences to these regimens. Adverse effects remain hypothetical in the face of potentially substantial mortality benefit.

“While we await further research, patients hospitalized with CAP should receive treatment with guideline-concordant antibiotic regimens covering both typical and atypical organisms.”

I recall, years ago, a patient who died in the hospital with CAP. She was a relatively young women and a good personal friend of mine. We struggled mightily to save her. Such patients are unforgettable.

I believe if we had the appropriate antibiotics and the present knowledge, we could have saved her.

The benefit / harm-cost ratio of combined antibiotics in severely ill patients with CAP is very high.

I would not let putative adverse effects deter me.

Not Only Continuing PA, But Also Initiating PA, Was Associated With Better Survival And Function.

9-2 PHYSICAL ACTIVITY, FUNCTION, AND LONGEVITY AMONG THE VERY OLD

This study examined the influence of physical activity (PA) among an aging cohort during 18 years of follow-up. Is PA in older adults, including the oldest old (85+ years) associated with better survival, and functional and health benefits?

Followed a cohort of residents in Jerusalem born in 1920-21 from age 70 at baseline (in 1990) to 2008

Eight year mortality (%)	Physically active	Sedentary
Age 70	15	27
Age 78	26	41
Age 85 (3-year mortality)	7	24

Adjusted hazard ratio of mortality from any cause according to level of PA:

	< 4 h/w	> 4 h/w	Walking daily	Sports twice weekly
Age 70-78	1.00 (referent)	0.69	0.42	0.47
78-85	1.00	0.67	0.60	0.57
85-88	1.00	0.26	0.29	0.19

Changing levels of PA and survival: Not only continuing PA (consistent), but also starting PA at age 70+ (increasers) was associated with better survival compared with continuing sedentary participants and these who decreased PA (decreasers):

Mortality from ages (%)	Age 70 to 88	Age 85 to 88
Continuing PA (consistent)	32	8
Increased PA (increasers)	41	13
Decreased PA (decreasers)	56	25
Consistent sedentary	52	25

One important finding was the sustained protective effect of PA against functional decline.

Physical activity level was associated with an independent functional status over time. Between ages 78-85, independence in performing activities of daily living deteriorated less in those who were physically active (27% of those who were physically active lost independent function vs 42% of those who were not physically active.)

“Maintaining function is a central goal in aging, and awareness is increasing of the intimate relationship between the phenotype of frailty, loss of physiological reserves, and performance-based measures on functional decline as harbingers of preterminal trajectories of illness and mortality.”

Among older people, PA may be instrumental in delaying the onset of the spiral of decline

through its influence on a spectrum of pathways, which may include improved cardiovascular fitness, decelerated sarcopenia, reduced adiposity, and improved immunity.

Conclusion: Among the very old, not only continuing, but also initiating PA was associated with better survival and function.

I enjoy articles providing information on benefits of lifestyle interventions. They are the backbone of primary care medicine.

The authors comment on reverse causality (Those whose state of health is good at old age would be more likely to exercise.) They discount this possibility.

Delayed The Need For Drug Therapy And Led To More Favorable Changes In Glycemic Control And Coronary Risk Factors

9-3 EFFECT OF A MEDITERRANEAN –STYLE DIET ON THE NEED FOR ANTI-HYPERGLYCEMIC DRUG THERAPY IN PATIENTS WITH NEWLY DIAGNOSED TYPE-2 DIABETES

Lifestyle intervention studies have demonstrated large reductions in risk for type-2 diabetes (**DM-2**).

The American Diabetes Association (**ADA**) recommends that patient with newly diagnosed DM-2 be treated with pharmacotherapy as well as lifestyle changes. The rationale for combined therapy is that each form of treatment alone is imperfect. Lifestyle changes are often inadequate because patients do not lose weight, or regain weight, or that their diabetes worsens independently of weight.

This randomized trial compared with effectiveness, durability, and safety of a low-carbohydrate mediterranean diet (**MD**) vs a low-fat ADA diet in patients with newly diagnosed DM-2.

Between 2004-2008 followed 215 overweight patients (mean age 52) with newly diagnosed DM-2. None had been treated with drugs. All were sedentary and had a stable weight over the past 6 months. At baseline, mean BMI = 30. HbA1c = 8%. All received education emphasizing the importance of a healthy diet and physical activity. (**PA**)

Randomized subjects to 1) a low-carbohydrate Mediterranean diet (**MD**), or 2) a low-fat ADA diet.

Mediterranean diet: rich in vegetables and whole grains, and low in red meat. Energy was restricted to 1500 kcal/d in women and 1800 in men, with a goal of a carbohydrate content of less than 50% of daily energy; and less than 30% of calories as fat. (The main source of fat was olive oil.)

ADA diet: Based on ADA guidelines. Rich in whole grains and reduced fat, sweets, and high-fat snacks. No more than 30% of energy from fat, and no more than 10% as saturated fat. Calorie restriction the same as the MD.

After 4 years:	MD	ADA-diet
Requiring drug treatment (%)	44	70 (Almost all with persistent HbA1c >7%)
BMI	- 1.2	-0.9
Waist circumference (cm)	- 3.0	-2.6
HbA1c (%)	-0.9	-0.5

The MD group also had slight advantages in serum insulin, lipids, systolic BP, total energy intake, and carbohydrate and fat intake.

Participants in both groups increased the time spent being physically active, with no statistical significant difference between groups.

Conclusion: Compared with an ADA low-fat diet, a low carbohydrate MD led to more favorable changes in glycemic control and coronary risk factors, and delayed the need for drug therapy in overweight patients with newly diagnosed DM-2.

Another illustration of the importance of lifestyle.

Non-Inferior Obvious Advantages More Expensive

9-4 DABIGATRAN versus WARFARIN IN PATIENTS WITH ATRIAL FIBRILLATION

Dabigatran etexilate is an oral pro-drug that is rapidly converted in serum to dabigatran, a potent direct competitor of thrombin. Serum half-life is 12 to 17 hours. The drug does not require regular monitoring.

Multi-country trial enrolled (2005-2007) over 18 000 participants (mean age = 71) who had AF and an increased risk of stroke.

Randomized to: 1) dabigatran 110 or 150 mg twice daily orally, or 2) adjusted-dose warfarin to a target INR of 2.0 to 3.0. Concomitant use of aspirin (< 100 mg daily) or other anticoagulant agents was permitted.

The primary analysis was whether either dose of dabigatran was inferior to warfarin. Median duration of follow-up = 2 years.

Primary outcomes (% per year)	Dabigatran (150 mg)	Warfarin
Stroke or systemic embolism	1.1	1.7
Hemorrhagic stroke	0.10	0.38
Death from any cause	3.64	4.13
Myocardial infarction	0.74	0.53
Pulmonary embolism	0.15	0.09

Adverse effects (% per year)

Major bleeding	3.1	3.4
GI bleeding	1.5	1.02
Minor bleeding	14.8	16.4
Intracranial bleeding	0.30	0.74
Discontinuation (at 2 years)	21	17

The investigators considered the net clinical benefit to favor dabigatran.

Conclusion: In patients with AF, dabigatran was associated with rates of stroke similar to those of warfarin. Rates of hemorrhage were similar. Dabigatran was considered non-inferior to warfarin

Dabigatran (Pradaxa) is approved in Europe and Canada. It is expensive. The dose is not settled.

This drug has many advantages. It could be used for many indications in which there is an increased likelihood of thromboembolism.

Will thrombin inhibitors supplant warfarin?

As a rule, I do not abstract articles about drugs until the drug is approved by the FDA, and is on the market in the USA. Dabigatran is so potentially important, I decided to abstract this article.

Ovarian Cancer Can No Longer Be Regarded As A Silent Killer.

9-5 DIAGNOSIS OF OVARIAN CANCER IN PRIMARY CARE

Ovarian cancer (OC) accounts for about 4% of all cancers in women. Overall 5-year survival is about 35%; stage I and II about 80-90%; stage III and IV about 25%.

Currently, only 30% are diagnosed in early stages.

There is no effective screening test. Presentation is usually to primary care.

This case-control study included women age over 40 between 2000-2007 in 39 primary care practices in England totaling over 66 000 patients aged 40-69, and 31 000 age 70 and over.

Identified 212 cases of OC (median age 67) by searching practice computer records. Five controls (n = 1060) were matched by age and practice. Studied symptoms occurring only in at least 5% of either cases or controls.

Seven clinical features remained in the final model:

	Cases n = 212 (%)	Controls n = 1066 (%)	Likelihood ratio
Abdominal distention	77 (36)	6 (0.6)	65
Loss of appetite	44 (21)	16 (1.5)	14
Postmenopausal bleeding	28 (13)	12 (1)	12

Abdominal bloating	35 (17)	21 (2)	8.4
Abdominal pain	112 (53)	92 (9)	6.2
Rectal bleeding	18 (8.5)	16 (1.5)	5.7
Urinary frequency	28 (14)	31 (2.9)	4.8
Physical signs:			
Abdominal mass	71(33)	1 (0,1)	360
Abdominal tenderness	51 (24)	19 (1.8)	14

“We calculated the risk of ovarian cancer across the whole range of important symptoms in the setting where diagnostic delays are most prevalent –primary care.”

“We found seven symptoms . . . that were independently associated with ovarian cancer.” Three of these symptoms –abdominal pain, abdominal distention, and urinary frequency—remained associated with OC when restricted to the period 6 months before diagnosis. (Ie, were present for longer than 6 months.)

Over half the women had a record of abdominal pain. It was equally common with early as for advanced OC. It was present for many months before diagnosis in some women. The likelihood ratio of abdominal pain was low. This is a classical conundrum in those working in primary care—the low risk, but not zero risk symptom. (Ie, women would not generally be offered investigation on the basis of abdominal pain alone.)

Conclusion: Currently, the only realistic proposition for expediting the diagnosis of OC rests with its identification in women with symptoms. Symptoms are common and often reported even in early and potentially curable cancers. In particular, abdominal distention is a common important symptom and warrants investigation. Ovarian cancer is not silent.

Between Two Levels Of Severity, Decision Is More Difficult. Patient Preference Is Important

9-6 NON-SURGICAL TREATMENT IN CARPAL TUNNEL SYNDROME

It is generally accepted that severe CTS, manifested by thenar eminence atrophy and severe sensory loss requires surgery. Surgeons do not usually encourage surgery in patients with mild symptoms, no functional limitation, or no neurological deficit.

Between these two levels of severity, the decision is more difficult.

A multicenter randomized trial entered 116 patients with idiopathic CTS, normal two point discrimination, and no thenar atrophy. Most had abnormal median nerve conduction tests and moderately severe disease.

Non-surgical treatment: Mainly hand exercises (ligament stretching and tendon gliding exercises) and wrist splinting. (Wrist splinting is the most common non-surgical treatment.) Most non-surgical patients received, to varying degrees, several of the non-invasive treatments available. Treatments were intensive, requiring repeated hand therapy. Non-improvers were offered ultrasound. (Hand-wrist exercises and ultrasound did not provide additional benefit beyond that offered by splinting alone.) There was a substantial non-adherence to those treatments. There was a large cross-over to surgery. Patients who do not have satisfactory improvement with non-surgical treatment should be offered surgery.

Surgery: Abundant evidence from randomized trials supports the high effectiveness of surgery (open or endoscopic tunnel release). Patient-reported measurements of functional status and symptom severity showed that surgery was significantly more efficacious than non-surgery at 6 and 12 months. The differences were modest (0.4 on 1-5 scale) on an intention-to-treat basis. Of the patients who actually underwent surgery, 88% had symptom improvement. Surgery results in rapid symptom relief. Non-surgery does not. At 6 months and at 12 months, surgery patients had less pain. And surgery, more often than splinting, results in complete recovery as opposed to improvement.

Patient preference is important. Faced with the need to wear a splint every night and during the daytime for weeks some might prefer surgery; others may prefer partial recovery to potential surgical risks.

The authors tilt toward surgery. I would not tarry too long with non-surgical treatments.

ABSTRACTS SEPTEMBER 2009

Cover Both Typical And Atypical Organisms

9=1 GUIDELINE-RECOMMENDED ANTIBIOTICS IN COMMUNITY-ACQUIRED PNEUMONIA: Not Perfect, but Good

Patients hospitalized with community-acquired pneumonia (CAP) can be infected with both typical and atypical bacteria. Clinical features at presentation are not specific enough to consistently predict the causative agent. Absent unique epidemiological characteristics, the overwhelming majority of patients must be treated empirically.

Guidelines¹ have been published recommending specific empirical antibiotic regimens:

For outpatients:

Previously healthy: A macrolide (azithromycin, or clarithromycin, or erythromycin).

For patients with co-morbidities:

- 1) Respiratory quinolone (levofloxacin, moxifloxacin, or gemifloxacin), or
- 2) A beta-lactam (amoxicillin, ampicillin, or methicillin) + a macrolide.

For inpatients or ICU:

- 1) Beta-lactam (ceftriaxime, ceftaxime, or ampicillin/sulbactam) + respiratory quinolone or azithromycin.

Nevertheless, controversy exists regarding the most appropriate initial antibiotics for hospitalized patients.

A growing body of evidence supports the use of empirical regimens to target both typical and atypical organisms.

Three retrospective cohort studies in different settings reported that patients who received guideline-concordant antibiotics had decreased in-hospital or 30-day mortality. Two large Medicare studies of elderly patients admitted with CAP also reported a lower 30-day mortality in patient treated with antibiotics compliant with guidelines. After attempts were made to control for potential confounders, benefits were significant. The absolute risk reduction averaged 5%. (NNT = 20).

“The evidence is not perfect by any means, but it is good.”

Some researchers contend that adding atypical organisms to management in the hospital should not be routine.

Two articles in this issue of Archives add to the literature regarding appropriate empirical use of antibiotics for CAP.^{2,3} They support the current guidelines.

. Why do fluoroquinolones, or the addition of macrolides to beta-lactams benefit? It may be related to the possibility that they target atypical organisms, especially *Legionella*. A recent international study reported that atypical organisms are relatively common, and cause up to 28% of cases of CAP.

For clinicians, the 2 studies add to the growing body of robust evidence supporting guideline-recommended antibiotic regimens. No research has documented clear negative consequences to these regimens. Adverse effects remain hypothetical in the face of potentially substantial mortality benefit.

“While we await further research, patients hospitalized with CAP should receive treatment with guideline-concordant antibiotic regimens covering both typical and atypical organisms.”

To paraphrase Voltaire—“We should not let the perfect be the enemy of the good.”

Archives Internal Medicine September 14, 2009; 169:1462-64 Editorial by Bradley A Sharpe, University of California, San Francisco.

1 Infectious Diseases Society of America and the American Thoracic Society consensus guidelines Clin Infect Dis 2007; 44(suppl 2) S27-S72 (Google search: I have expanded the treatment indications beyond those mentioned in the editorial following a computer search of the guidelines RTJ.)

2 “Improving outcomes in elderly patients with community-acquired pneumonia by adhering to national guidelines” Archives Int Med September 2009; 169: 1515-24 Original investigation, first author Forest W Arnold, University of Louisville School of Medicine, Louisville KY.

A secondary analysis of a database of patients age 65 and older who were hospitalized for CAP. Initial empiric therapy was evaluated for compliance according to the 2007 guidelines; 975 were given antimicrobial regimens adherent to the guidelines; 660 patient were treated with non-adherent regimens.

Adherence was associated with a statistically significant decreased time to achieve clinical stability by 7 days (71% vs 57%), shorter length of stay (median 8 days vs 10 days), and decreased overall in-hospital mortality (8% vs 17%).

3 “Guideline-concordant therapy and reduced mortality and length of stay in adults with community-acquired pneumonia” Archives Internal Medicine September 14, 2009; 169: 1525-31 First author Caitlin McCabe, Hospital for Sick Children, Toronto, Ontario, Canada.

Evaluated the impact of 2007 guideline-concordant therapy on over 54 000 multicenter hospitalized patients; 65% received initial guideline-concordant therapy.

After adjustment of confounders, guideline-concordant therapy was associated with decreased hospital mortality (odds ratio = 0.77), sepsis (OR 0.83), renal failure (OR 0.79). Length of stay and duration of parenteral therapy were reduced by approximately 0.6 days.

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Not Only Continuing PA, But Also Initiating PA, Was Associated With Better Survival And Function.

9-2 PHYSICAL ACTIVITY, FUNCTION, AND LONGEVITY AMONG THE VERY OLD

Physical activity (PA) is a modifiable lifestyle behavior associated with improved health, functional status, and longevity. It is an established public health goal. Most research has focused on middle-age populations. Recommendations for PA set no upper age limits.

This study examined the influence of PA among an aging cohort during 18 years of follow-up. Is PA in older adults, including the oldest old (85+ years) associated with better survival, and functional and health benefits?

STUDY

1. Followed a cohort of residents in Jerusalem born in 1920-21 from age 70 at baseline (in 1990) to 2008. The phase I cohort was augmented with new participants at phases II and III.
Phase I age 70 (n = 605)
Phase II age 78 (n = 1021)
Phase III age 85 (n = 1222)
2. All underwent comprehensive home assessment at ages 70,78, and 85. Gathered data concerning PA, medical history, and cognitive and psychological status.
3. Determined data on mortality, health, and functional status at ages 70 to 85.
4. Primary outcome = death. Secondary outcomes = deterioration over time in functional status, health measures, and new disease onset.

RESULTS

1. Eight year mortality (%)	Physically active	Sedentary
Age 70	15	27
Age 78	26	41
Age 85(3-year mortality)	7	24

2. Adjusted hazard ratio of mortality from any cause according to level of PA:

	< 4 h/w	> 4 h/w	Walking daily	Sports twice weekly
Age 70-78	1.00 (referent)	0.69	0.42	0.47
78-85	1.00	0.67	0.60	0.57
85-88	1.00	0.26	0.29	0.19

3. Changing levels of PA and survival: Not only continuing PA (consistent), but also starting PA

at age 70+ (increasers) was associated with better survival compared with continuing sedentary participants and those who decreased PA (decreasers):

Mortality from ages (%)	Age 70 to 88	Age 85 to 88
Continuing PA (consistent)	32	8
Increased PA (increasers)	41	13
Decreased PA (decreasers)	56	25
Consistent sedentary	52	25

4. Physical activity level was associated with an independent functional status over time. Between ages 78-85, independence in performing activities of daily living deteriorated less in those who were physically active (27% of those who were physically active lost independent function vs 42% of those who were not physically active.)
5. During follow-up during ages 70-78, and 79-85, physically active participants reported less onset of loneliness, and better self-rated health.

DISCUSSION

1. “This 18-year longitudinal cohort study supports the hypothesis that, not only continuing, but also initiating, PA among older people delays functional loss and improves survival.”
2. The magnitude of difference between physically active and sedentary participants actually increased with advancing age. Maximum survival benefit was observed among the oldest age group.
3. One important finding was the sustained protective effect of PA against functional decline. “Maintaining function is a central goal in aging, and awareness is increasing of the intimate relationship between the phenotype of frailty, loss of physiological reserves, and performance-based measures on functional decline as harbingers of preterminal trajectories of illness and mortality.”
4. Among older people, PA may be instrumental in delaying the onset of the spiral of decline through its influence on a spectrum of pathways, which may include improved cardiovascular fitness, decelerated sarcopenia, reduced adiposity, and improved immunity.
5. Not only is PA protective among people who remain active throughout their lives into old age, but becoming active during advanced old age is also beneficial even among previously sedentary people.
6. It may be argued that reversed causality is at work (PA serves as a proxy for good health). However, the association remained significant after adjustment for comorbidities, functional status,

and self-rated health status.

7. “The fact that PA still remains an independent predictor suggests that activity of at least 4 hours per week, daily walking, or participating in sports twice weekly is beneficial in older adults.”

CONCLUSION

Among the very old, not only continuing, but also initiating PA was associated with better survival and function.

Archives Int Med September 14, 2009; 169: 1476-83 Original investigation, first author Jochanan Stressman, Hadassah Hebrew University Medical Center, Jerusalem, Israel. The Jerusalem Longitudinal Cohort Study

Delayed The Need For Drug Therapy And Led To More Favorable Changes In Glycemic Control And Coronary Risk Factors

9-3 EFFECT OF A MEDITERRANEAN –STYLE DIET ON THE NEED FOR ANTI-HYPERGLYCEMIC DRUG THERAPY IN PATIENTS WITH NEWLY DIAGNOSED TYPE-2 DIABETES

Lifestyle intervention studies have demonstrated large reductions in risk for type-2 diabetes (**DM-2**).

The American Diabetes Association (**ADA**) recommends that patients with newly diagnosed DM-2 be treated with pharmacotherapy as well as lifestyle changes. The rationale for combined therapy is that each form of treatment alone is imperfect. Lifestyle changes are often inadequate because patients do not lose weight, or regain weight, or that their diabetes worsens independently of weight.

Pharmacotherapy often fails with time.

Mediterranean –style diets (**MD**), with a high proportion of mono-unsaturated fat, provide cardiovascular benefits and increase insulin sensitivity. The ADA recommends low-carbohydrate or low fat calorie-restricted diet in overweight patients with DM-2.

This randomized trial compared with effectiveness, durability, and safety of a low-carbohydrate MD vs a low-fat ADA diet in patients with newly diagnosed DM-2.

STUDY

1. Between 2004-2008 followed 215 overweight patients with newly diagnosed DM-2. None had been

treated with drugs. All were sedentary and had a stable weight over the past 6 months. At baseline, mean BMI = 30. HbA1c = 8%; age = 52.

2. All received dietary education emphasizing the importance of a healthy diet and physical activity. (PA) All successfully self-monitored their diet and PA over a 2-week run-in period. They were taught to prepare their own meals at home. Periodically, nutrition advice was given by dietitians, and HbA1c was measured. Subjects kept a food diary.
3. Randomized subjects to 1) a low-carbohydrate MD, or 2) a low-fat ADA diet.
4. Mediterranean diet: The MD was rich in vegetables and whole grains, and low in red meat. Energy was restricted to 1500 kcal/d in women and 1800 in men, with a goal of a carbohydrate content of less than 50% of daily energy; less than 30% of calories as fat. (The main source of fat was olive oil.)
5. ADA diet: Based on ADA guidelines. Rich in whole grains and reduced fat, sweets, and high-fat snacks. No more than 30% of energy from fat, and no more than 10% as saturated fat. Calorie restriction the same as the MD.
6. All received guidance on increasing physical activity level (175 minutes of moderate-intensity per week).
7. Primary outcome = time to introduction of anti-hyperglycemic drugs. Subjects with a HbA1c level greater than 7% were given 3 months to reinforce diet and PA. If HbA1c continued over 7%, a drug regimen was introduced.
8. Secondary outcome = changes in weight, HbA1c, glucose, serum insulin, and coronary risk factors.
9. Goals = HbA1c under 7%, BP < 130.80, LDL-cholesterol < 100 mg/dL.
10. Analysis by intention-to-treat. Follow-up = 4 years.

RESULTS

1. After 4 years:	MD	ADA-diet
% requiring drug treatment (%)	44	70 (Almost all with persistent HbA1c >7%)
BMI	- 1.2	-0.9
Waist circumference (cm)	- 3.0	-2.6
HbA1c (%)	-0.9	-0.5
Serum insulin (pmol/L)	-9.8	-5.6
Total cholesterol (mg/dL)	-10	-4
HDL-cholesterol (mg/dL)	+4	+1

Triglycerides (mg/dL)	-11	-3
Systolic BP (mmHg)	-2.5	-1.0
Total energy (kcal/d)	-450	-409
Carbohydrate (%)	-7.9	- 0.1
Saturated fat (%)	-0.2	-0.4
Monounsaturated fat (%)	+5.5	-1.0
Polyunsaturated fat (%)	+2.6	-1.1

2. Participants in both groups increased the time spent being physically active, with no statistical significant difference between groups.

DISCUSSION

1. The MD delayed the need for drug therapy, without any difference in PA between the MD and ADA. MD was associated with greater weight loss.
2. “Analysis adjusted for weight change suggested a statistically significant reduced rate of needing drug therapy, so the effect of the MD goes beyond weight reduction.”
3. Prospective studies have shown that the MD is associated with reduction in risk for DM-2. And a reduction in risk of overall mortality from cardiovascular disease. One of the most desirable features of the MD is improvement in cardiovascular risk factors.

CONCLUSION

Compared with a ADA low-fat diet, a low carbohydrate MD led to more favorable changes in glycemic control and coronary risk factors, and delayed the need for drug therapy in overweight patients with newly diagnosed DM-2.

Annals Internal Medicine September 1, 2009; 151: 306-14 Original investigation, first author Catherine Esposito, Second University of Naples, Italy.

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Non-Inferior Obvious Advantages More Expensive

9-4 DABIGATRAN versus WARFARIN IN PATIENTS WITH ATRIAL FIBRILLATION

Dabigatran etexilate is an oral pro-drug that is rapidly converted in serum to dabigatran, a potent direct competitor of thrombin. Serum half-life is 12 to 17 hours. The drug does not require regular monitoring.

This trial compared the long-term effect of two doses of dabigatran vs warfarin in patients with atrial fibrillation (AF).

STUDY

1. Multi-country trial enrolled (2005-2007) over 18 000 participants (mean age = 71; mean CHADs score¹ = 2.1) who had AF and a risk of stroke. All had at least one other risk factor: previous stroke or TIA, left ventricular ejection fraction less than 40%, NYHA class II or higher heart failure symptoms within 6 months, and an age of at least 75, or an age of 65 to 74 with diabetes, hypertension, or coronary artery disease. None had a condition increasing risk of hemorrhage. or a creatinine clearance < 30 mL per minute.
2. Randomized to: 1) dabigatran 110 or 150 mg twice daily² orally, or 2) adjusted-dose warfarin to a target INR of 2.0 to 3.0. Concomitant use of aspirin (< 100 mg daily) or other anticoagulant agents was permitted.
3. Primary outcome = stroke or systemic embolism. The primary net benefit outcome = composite of stroke, systemic embolism, pulmonary embolism, myocardial infarction, death, or major hemorrhage. Defined major bleeding as a reduction in hemoglobin be at least 20 g/L, transfusion of at least 2 units of blood, or symptomatic bleeding into a critical organ.
4. The primary analysis was whether either dose of dabigatran was inferior to warfarin. Median duration of follow-up = 2 years.

RESULTS

1. Aspirin was used continuously in about 20% of participants.
2. Mean INR for those taking warfarin was within therapeutic range 64% of the time.

3. Primary outcomes (% per year)	Dabigatran (150 mg)	Warfarin
Stroke or systemic embolism	1.1	1.7
Hemorrhagic stroke	0.10	0.38
Death from any cause	3.64	4.13
Myocardial infarction	0.74	0.53
Pulmonary embolism	0.15	0.09
4. Adverse effects (% per year)		
Major bleeding	3.1	3.4
GI bleeding	1.5	1.02
Minor bleeding	14.8	16.4

Intracranial bleeding	0.30	0.74
Discontinuation (at 2 years)	21	17

5. Liver dysfunction (enzymes over 3 times normal) did not occur more commonly with dabigatran than with warfarin.
6. The only adverse effect that was significantly more common with dabigatran than with warfarin was dyspepsia.
7. Net clinical benefit (% per year: composite of stroke, systemic embolism, pulmonary embolism, myocardial infarction, death, and major bleeding: dabigatran 150 mg vs warfarin (6.9 vs 7.6) (The investigators consider this an advantage for dabigatran. RTJ)

DISCUSSION

1. Dabigatran was non-inferior to warfarin with respect to the primary efficacy outcome of stroke and systemic embolism. (Dabigatran 150 mg was slightly superior to warfarin in reducing stroke. Relative risk vs warfarin = 0.66; absolute difference = 0.58; NNT = 172)³
2. The lower risk of intracranial hemorrhage related to dabigatran vs warfarin may be a major advantage.
3. The twice-daily dosage of dabigatran reduces variability in the anticoagulation effect, especially as compared with warfarin, which is difficult to control.
4. Warfarin broadly inhibits coagulation (inhibiting factors II, VII, IX, and X and proteins C and S. By selectively inhibiting only thrombin, dabigatran may have antithrombotic efficacy while preserving some other hemostatic mechanisms in the coagulation system and thus potentially mitigating the risk of bleeding.

CONCLUSION

In patients with AF, dabigatran was associated with rates of stroke similar to those of warfarin. Rates of hemorrhage were similar. Dabigatran was considered non-inferior to warfarin

NEJM September 17, 2009; 361: 1139-51 Original investigation, first author Stuart J Connolly, McMaster University, Hamilton, Ontario, Canada The Randomized Evaluation of Long-term Anticoagulation Therapy trial (RE-LY)

Supported by Boehringer Ingelheim

1 CHADs score = a measure of the risk of stroke in which congestive heart failure, hypertension, age 75 and older, diabetes, and history of stroke or TIA. Each one point adding up to a total of 6.

2 The study used 2 different doses of dabigatran 110 mg and 150 mg. For simplicity, I omit the 110 mg group. (150 seemed slightly superior in reducing risk of stroke.)

3. My calculation RTJ

Ovarian Cancer Can No Longer Be Regarded As A Silent Killer.

9-5 RISK OF OVARIAN CANCER IN WOMEN WITH SYMPTOMS IN PRIMARY CARE

Ovarian cancer (OC) accounts for about 4% of all cancers in women. Overall 5-year survival is about 35%; stage I and II about 80-90%; stage III and IV about 25%.

Currently, only 30% are diagnosed in early stages.

There is no effective screening test.

The main prospect of early diagnosis is improved identification of symptomatic cancer.

Presentation is usually to primary care.

Until recently OC has been considered to have few symptoms—a “silent killer”. Several recent studies have shown that symptoms are common, but often unrecognized. The symptoms that have been identified are also common in non-malignant conditions. As many as 95% of women with OC have a symptom potentially representing OC.

STUDY

1. This case-control study included women age over 40 between 2000-2007 in 39 primary care practices in England totaling over 66 000 patients aged 40-69, and 31 000 age 70 and over.
2. Identified 212 cases of OC (median age 67) by searching practice computer records. Five controls (n = 1060) were matched by age and practice. Studied symptoms occurring only in at least 5% of either cases or controls.

RESULTS

1. Cases had consulted a median total of 10 times; controls, 6 times.
2. Seven clinical features remained in the final model:

	Cases n = 212 (%)	Controls n = 1066 (%)	Likelihood ratio
Abdominal distention	77 (36)	6 (0.6)	65
Loss of appetite	44 (21)	16 (1.5)	14
Postmenopausal bleeding	28 (13)	12 (1)	12
Abdominal bloating*	35 (17)	21 (2)	8.4

Abdominal pain	112 (53)	92 (9)	6.2
Rectal bleeding	18 (8.5)	16 (1.5)	5.7
Urinary frequency	28 (14)	31 (2.9)	4.8

(*Few studies define the difference between abdominal distention and bloating. Distention is a progressive increase in size; bloating is alternating increases and decreases in girth.)

3. Of the 7 symptoms listed, 85% of cases and 16% of controls had at least one.

4. Physical signs:

Abdominal mass	71(33)	1 (0,1)	360
Abdominal tenderness	51 (24)	19 (1.8)	14

6. All symptoms except urinary frequency were more common in patients over age 70, reflecting the higher incidence of OC in older women.

7. Several symptoms were present before the last 6 months preceding the diagnosis of OC: abdominal pain, abdominal distention, and urinary frequency.

DISCUSSION

1. “We calculated the risk of ovarian cancer across the whole range of important symptoms in the setting where diagnostic delays are most prevalent –primary care.”

2. “We found seven symptoms . . . that were independently associated with ovarian cancer.” Three of these symptoms –abdominal pain, abdominal distention, and urinary frequency—remained associated with OC when restricted to the period 6 months before diagnosis. (Ie, were present for longer than 6 months.)

3. Interview studies suggest that only 7% of women with OC truly have no symptoms.

4. If abdominal distention were included in guidelines for urgent investigation, some women could have their diagnosis expedited by many months.

5. Even if true intermittent distention (bloating) does carry some risk, it is considerably less than persistent distention.

6. Over half the women had a record of abdominal pain. It was equally common with early as for advanced OC. It was present for many months before diagnosis in some women. The likelihood ratio of abdominal pain was low. This is a classical conundrum in those working in primary care—the low risk, but not zero risk symptom. (Ie, women would not generally be offered investigation on the basis of abdominal pain alone.)

7. The records rarely pinpointed the exact site of pain, so it was not known if lower abdominal pain or pelvic pain was particularly linked to OC.

8. Urinary frequency was relatively uncommon compared with abdominal distention or pain, and posed less risk than either, but OC must be remembered as a diagnostic possibility in patients developing urinary frequency.
9. Most reporting of symptoms to general practitioners occurs in the 3 months before diagnosis. Earlier diagnosis is possible in some women.
10. Unlike abdominal distention, pain, and urinary frequency, postmenopausal and rectal bleeding are indications for urgent investigation, although OC is not the prime concern.

CONCLUSION

Currently, the only realistic proposition for expediting the diagnosis of OC rests with its identification in women with symptoms. Symptoms are common and often reported even in early and potentially curable cancers.

In particular, abdominal distention is a common important symptom and warrants investigation. Ovarian cancer is not silent.

BMJ 2009;339:b2998 doi:10.1136/bmj.b2998 Original investigation, first author William Hamilton, University of Bristol, Bristol, UK

A brief abstract was presented in the print issue of BMJ September 12, 1009; 339: 616

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Between Two Levels Of Severity, Decision Is More Difficult. Patient Preference Is Important

9-6 NON-SURGICAL TREATMENT IN CARPAL TUNNEL SYNDROME

Carpal tunnel syndrome (CTS) is a common cause of disabling hand symptoms. Surgical and non-surgical therapy are offered. In 2000, in the UK, about 1/3 of patients newly presenting in primary care with CTS were treated surgically. It is generally accepted that severe CTS, manifested by thenar eminence atrophy and severe sensory loss requires surgery. Surgeons do not usually encourage surgery in patients with mild symptoms, no functional limitation, or no neurological deficit.

Between these two levels of severity, the decision is more difficult.

Local steroid injection is used, but efficacy beyond one month has not been established.

A multicenter randomized trial reported in *Lancet*¹ entered 116 patients with idiopathic CTS, normal two point discrimination, and no thenar atrophy. Most had abnormal median nerve conduction tests and moderately severe disease.

Non-surgical treatment: Mainly hand exercises (ligament stretching and tendon gliding exercises) and wrist splinting. (Wrist splinting is the most common non-surgical treatment.) Most non-surgical patients received, to varying degrees, several of the non-invasive treatments available. Treatments were intensive, requiring repeated hand therapy. Non-improvers were offered ultrasound. (Hand-wrist exercises and ultrasound did not provide additional benefit beyond that offered by splinting alone.)

There was a substantial non-adherence to those treatments.

There was a large cross-over to surgery.

The mean functional status score at baseline in non-surgical patients remained almost unchanged at 6 months, and showed relatively small improvement at 12 months. Almost half the patients who had not undergone surgery continued to have high symptom severity.

Patients who do not have satisfactory improvement with non-surgical treatment should be offered surgery.

It may be argued that these results could still justify initial wrist splinting in view of the fact that about 60% of non-surgical patients had not required surgery after 12 months, and the difference in symptom severity scores between surgery and non-surgery were moderate. Initial non-surgical treatment has advantages. It is appropriate when symptom duration is short and diagnosis is less certain.

Surgery: Abundant evidence from randomized trials supports the high effectiveness of surgery (open or endoscopic tunnel release).

Patient-reported measurements of functional status and symptom severity showed that surgery was significantly more efficacious than non-surgery at 6 and 12 months. The differences were modest (0.4 on 1-5 scale) on an intention-to-treat basis.

Of the patients who actually underwent surgery, 88% had symptom improvement.

Surgery results in rapid symptom relief. Non-surgery does not. At 6 months and at 12 months, surgery patients had less pain. Surgery, more often than splinting, results in complete recovery as opposed to improvement.

Surgery can be followed by prolonged work disability. Persistent pain 5-years after surgery has been reported in 6%.

This should not imply that, in patients with moderately severe symptoms, physicians should always advocate surgery without initial non-surgical treatment.

Patient preference is important. Faced with the need to wear a splint every night and during the daytime for weeks some might prefer surgery; others may prefer partial recovery to potential surgical risks.

What about diagnostic MRI? The results of MRI seem discordant with those of nerve conduction. The high rate of normal MRI suggests it would not be a useful diagnostic test.

Lancet September 26, 2009L 374: 1042-43 Editorial, first author Isam Atroshi, Lund University, Lund, Sweden.

1 “Surgery versus non-surgical therapy for carpal tunnel syndrome: A randomised parallel trial”

First author Jeffrey G Jarvik, University of Washington, Seattle, USA

Interpretation: “Symptoms in both groups improved, but surgical treatment led to better symptom outcome than did non-surgical treatment. However, the clinical relevance of this difference was modest. Overall, our study confirms that surgery is useful for patients with carpal tunnel syndrome without denervation.”

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