PRACTICAL POINTERS

FOR

PRIMARY CARE MEDICINE

ABSTRACTED MONTHLY FROM THE JOURNALS

A Free Public-service Publication

JUNE 2014

JAMA, NEJM, the BMJ, LANCET
JAMA INTERNAL MEDICINE
ANNALS INTERNAL MEDICINE

PUBLISHED BY PRACTICAL POINTERS, INC.
EDITED BY RICHARD T. JAMES JR. MD
400 AVINGER LANE, SUITE 203
DAVIDSON NC 28036 USA
www.practicalpointers.org

29th YEAR OF PUBLICATION

Practical Pointers is published every month on the internet as a public service.

The complete content of all issues for the past 10 years can be accessed at

www.practicalpointers.org

It is also available on a more timely basis by e-mail attachment. It contains no advertising. It is completely without bias. There is never any charge.

Requests for "subscription" to rjames6556@aol.com

I hope you will find *Practical Pointers* interesting and helpful.

Richard T. James Jr. M.D.

Editor/Publisher.

The editor thanks

Lois M. James for proof reading

Matthew Ramirez for internet application

6-1 ASSOCIATION BETWEEN INTENSIFICATION OF METFORMIN TREATMENT WITH INSULIN VS METFORMIN WITH SULFONYLUREAS AND CARDIOVASCULAR EVENTS (CVE) AND ALL-CAUSE MORTALITY AMONG PATIENTS WITH DIABETES:
Retrospective Cohort Study

The ADA recommends that, for patients with preserved renal function, treatment begin with metformin and lifestyle changes.

Often patients will require a second drug to reach treatment goals, but there is no consensus regarding which medication to use: insulin, sulfonylureas, or other drugs.

This study compared incidence of CVE or death among patients who intensified their metformin treatment with a sulfonylurea or insulin. The investigators hypothesized that intensification of metformin treatment with insulin would be associated with a lower risk compared with metformin intensified with sulfonylureas due to the superiority of insulin in achieving glucose control.

STUFY

1. Retrospective cohort study of VA patients with diabetes initially treated with metformin from 2001 to 2011 (n = 72 868)
2. Taking metformin + insulin (M + I; n = 2938). Taking metformin + sulfonylureas (M + S; n = 39 990).
3. The investigators selected 2436 individuals from the M + I group and matched them with propensity scores with 12 180 individuals taking M + S. (Each patient receiving added insulin was matched to 5 patients receiving added sulfonylurea.)
4. Primary outcome = a composite of acute myocardial infarction, hospitalization for stroke, and death.

RESULTS

1. Mean follow-up after intensification was 14 months
2. At baseline, compared with those adding a sulfonylurea, those receiving added insulin had higher HbA1c levels and higher prevalence of co-morbidities. The prevalence of those receiving insulin increased over time.
3. At one year, median HbA1c levels declined to 7% among M + I users, and to 6.9% among M + S users.
4. Relative hazards of CVE—acute myocardial infarction, hospitalization for stroke, or death per 1000 person-years:
   M + I 42.7
   M + S 32.9
   Adjusted hazard ratio (M + I / M + S = 1.30)
5. For all-cause deaths, 33.7 and 22.7 per 1000 person-years. (Adjusted HR = 1.44)

DISCUSSION

1. Among patients with diabetes who were taking metformin, the addition of insulin compared with addition of a sulfonylurea, was associated with an increased hazard of a composite of nonfatal cardiovascular outcomes and all-cause mortality.
2. There is consensus that metformin is first-line diabetes treatment. However, uncertainty remains regarding added therapy when metformin provides inadequate control. Addition of either I or S is considered a high-efficacy strategy with reasonable costs. S is used predominantly.
3. Two large RCTs demonstrated that regimens including greater use of insulin and tighter control did not reduce CVE compared to standard care.
4. The ACCORD trial randomized patients to intensive control (HbA1c < 6%) or standard care. 77% of

participants in the intensive treatment group received insulin vs 55% in the control group. The trial was stopped when the analysis found more all-cause mortality in the high-insulin group (5% vs 4%). Most excess mortality was due to CVE.

5. Several observational studies have reported no cardiovascular benefit of insulin vs noninsulin comparators. Some have reported worse outcomes among insulin recipients.
6. No other similar studies found an advantage of insulin compared with oral agents for risk of CVE. Several reported increased risk of weight gain and hypoglycemia associated with insulin.
7. Although insulin is a reasonable option for patients with high glucose levels, most patients prefer to delay insulin initiation.
8. The statistical significance of the primary outcome was driven by all-cause mortality. A clinically significant cardiovascular benefit could not be excluded.

CONCLUSION

Among patients with diabetes who were receiving metformin, the addition of insulin, compared with addition of a sulfonylurea, was associated with an increased risk of a composite of nonfatal cardiovascular outcomes and all-cause mortality.

JAMA June 11, 2014; 411:2288-96 doi:10.1001/jama.2014.4312
Original investigation, first author Christianne L Rounie, VA-Tennessee Valley Healthcare System Geriatric Research Education Clinical Center, Nashville. .

This is not a strong study. But I believe the conclusion is correct.

I welcomed the opportunity to learn about propensity score matching. (PSM)

PSM is a statistical matching technique of observational studies. (By definition, observational studies are not randomized.) PSM attempts to reduce the effects due to confounding variables. It is a balancing score. The distribution of observed baseline covariates will be similar between treated and controls.

A propensity score is the probability of a unit (eg, a person) being assigned to a particular treatment given the set of observed covariates. (Person A is matched with a person B on the basis of having the same biases that may possibly affect outcome). It is an attempt to equate the characteristics of two groups—treatment vs control, or in the above study M + I and M + S.

In randomized, controlled trials, the randomization process enables an unbiased estimation of treatment effects for each covariate. Randomization implies that treatment groups will be balanced on average by the law of large numbers.

Source—Wikipedia and "An Introduction to Propensity Score Methods for Reducing the Effects of Confounding in Observational Studies" by Paul C Austin, University of Toronto.

(See Practical Pointers May 2014 for a description of adverse effects of insulin-related-hypoglycemia. Some of the deaths in the M + I group must have been due to hypoglycemia.

An extreme example of PSM would be to gather a large number of identical twins and place them into 2 categories for study. Confounding variables between the two groups would be lessened. Ed.)

6-2 ADVERSE EFFECTS OF MARIJUANA USE

Legislation permitting marijuana for medical and recreational purposes is increasing. Patients may be asking physicians about its potential benefits and harms.

The popular notion seems to be that marijuana is a harmless pleasure to which access should not be regulated or considered illegal.

Currently, about 12% of people in the USA age 12 and over report using it in the past year. Use is highest among younger people. The most common route of administration is by inhalation. Marijuana can also be used to brew tea.

Regular use during adolescence is of particular concern since use by this age group is associated with deleterious consequences.

Multiple studies have reported detrimental effects.

But some studies have not. Whether it is harmful or not remains a subject of heated debate.

This is a review of the current state of the science related to the adverse health effects of the recreational use of marijuana, focusing on those for which the evidence is strongest.

1. Risk of addiction:

The evidence indicates that long-term use can lead to addiction. Indeed, about 9% of those who experiment with it become addicted (according to the criteria of DSM-IV) an estimated total of 2.7 million. The number goes up to about 1 in 6 among those who start smoking as teenagers, and to 25% to 50% among those who smoke daily.

There is also a bone fide cannabis withdrawal syndrome, which makes cessation difficult and relapse common.

2. Effect on brain development:

The brain continues to develop up to about age 21. During this time it is more vulnerable than the mature brain to adverse long-term effects of environmental insults such as exposure to tetra-hydro-cannabinol (THC) the primary active ingredient of marijuana.

As compared with unexposed controls, adults who smoked marijuana regularly during adolescence had impaired neural connectivity (fewer fibers) in specific brain regions. This may impair memory, learning, and executive function.

3. Possible role as a gateway drug:

Epidemiological data suggest that the use of marijuana in adolescence could influence multiple addictive behaviors in adulthood.

However, an alternative explanation is that people who are susceptible to drug-taking are more likely to start with marijuana.

4. Relation to mental illness:

Regular use is associated with increased risk of anxiety and depression, but causality has not been established. It also has been linked to schizophrenia, especially in young people with a genetic vulnerability.

5. Effect on school performance and lifetime achievement:

In 2013, the Monitoring the Future survey of high-school students found that 6.5% of students in grade 12 reported daily or near-daily use. (Probably an underestimate since those who drop out of school may have high rates of frequent use.)

The evidence suggests that such use results in measurable and long-lasting cognitive impairment. There is an association between use and poor grades.

Some studies suggest that long-tem effects may be reversible. Others show that long-term use results in permanent memory impairment.

Heavy use has been linked to lower income, unemployment, criminal behavior and lower satisfaction in life.

6. Risk of automobile accidents:

Both immediate and long-term exposure to marijuana impairs driving ability. Marijuana is the illicit drug most frequently reported in connection with impaired driving and accidents, including fatalities. The risk associated with the use of alcohol combined with marijuana appears to be greater than that associated with either drug alone.

There is a relationship between blood THC concentrations and performance in controlled driving studies. Persons with high blood levels of THC are 3 to 7 times as likely to be responsible for an automobile accident as persons who have not used the drug or alcohol before driving.

The combination of alcohol + marijuana is a greater risk.

7. Risk of cancer and other effects on health:

Marijuana smoking is associated with inflammation of the large airways, increased airway resistance, and lung hyperinflation. However, the long-term effect of low levels of exposure does not appear to be significant. The effect of long-term use on incidence of lung cancer is not clear. Smoking tobacco cigarettes in addition is a confounding factor.

LIMITATIONS OF THE EVIDENCE AND GAPS IN KNOWLEDGE:

Most of the effects of use reported here have been observed among heavy and long-term users.

Multiple confounding factors (including use combined with other drugs) detract from ability to establish causality.

Our understanding of the long-term effects of use during pregnancy in humans is poor.

The THC content of marijuana had been steadily increasing from 3% in the 1980s to 12% in 2012. This raises concerns that the consequences of marijuana may be worse now than in the past. This may account for the increase in ED visits and in fatal automobile accidents. It also raises questions about the findings of older studies on adverse effects.

There is a also a need to improve understanding of how to harness the potential benefits of marijuana without exposing sick people to intrinsic risks. The Institute of Medicine acknowledges the potential of marijuana smoking to stimulate appetite, especially in patients with AIDS and the related wasting syndrome, and on combating nausea due to chemotherapy for cancers, for severe pain, and some forms of spasticity. There are also reports of benefit for glaucoma.

We do not have a clear understanding of the effects of second-hand exposure to marijuana smoke.

Some physicians continue to prescribe marijuana despite limited evidence of benefit.

CONCLUSION:

Marijuana has been associated with substantial adverse effects with a high level of confidence. These include: addiction, diminished lifetime achievement, motor vehicle accidents, and symptoms of chronic bronchitis.

During intoxication, it can interfere with cognitive function and motor function.

Repeated use during adolescence may result in long-lasting changes in brain function.

The effects of the drug on individual health are determined, not only by its pharmacological properties, but also by its availability and social acceptability. Legal drugs (marijuana, alcohol, and tobacco) offer a sobering perspective, accounting for the greatest burden of disease associated with drugs, not because they are more dangerous than illegal drugs, but because the legal status allowa a more widespread exposure.

NEJM June 5, 2014:370:2219-27 doi:10.1056/NEJMMra1402309
Review Article, first author Nora D Volkow, National Institutes of Drug Abuse, National Institutes of Health, Bethesda MDB

The article gives 77 citations.
I believe this is a fair assessment of the present evidence.
Legal use is a social experiment. Will it last? I hope not.

==========

6-3 STROKE PREVENTION IN WOMEN: Synopsis of the 2014 American Heart Association/American Stroke Association Guidelines

An estimated 6.8 million persons in the US have had a stroke. The majority are women. At the time of stroke, women are older and are more likely to be living alone and have worse pre-morbid status than men. After stroke, they are more likely to be institutionalized and to have a poor recovery and worse quality-of-life.

There are unique risk factors for stroke in women: Pregnancy complications, hormonal contraception, and hormone therapy. Other risk factors more common in women: Hypertension, atrial fibrillation, migraine with aura, depression and psychological stress.

With these issues in mind, the AHA/ASA developed a sex-specific guideline consolidating recommendations specific for stroke prevention in women from experts in 14 different disciplines based on the English literature 1990-2013.

RECOMMENDATIONS

1. Risk factors for stroke:

A. Hypertension:

Hypertension is the most modifiable risk factor. It is more prevalent in women. It is often poorly controlled in older women. (Only 23% of women vs 38% of men over age 80 have BP less than 140/90.) There is currently no evidence that anti-hypertension treatment differentially affects BP response or stroke prevention by sex. But there are major evidence gaps about appropriate drug choices, treatment resistance, and adherence.

B. Atrial fibrillation: (AF)

There is a higher prevalence and associated risk for thrombo-embolic events in women. The CHADS2-VASc score gives an additional point for women. Women over age 75 should be actively screened for AF. Women age 65 and younger with lone AF should be treated with anti-platelet therapy.

C. Migraine with Aura:

Women are 4 times more likely than men to have migraine. Although the absolute risk for stroke associated with migraine is low, the association between migraine with aura is strongest in women younger than 55. Increased frequency may also be associated with stroke. The guideline therefore suggests reducing the frequency as a possible strategy to reduce risk, although there is no evidence that specific treatment strategies (calcium blockers, beta-blockers, and anti-epileptic drugs) reduce stroke risk. Given the synergistic relationship between smoking and migraine, smoking should be discontinued. Use of oral contraceptives should be discouraged.

D. Hormonal Contraception:

Is a risk factor for young women, increasing risk by 1.4- to 2.0-fold compared with women who do not use it.

The absolute risk is low (2 events per 100 000 per year) with the use of the lowest dose. Risk rises exponentially to 65 per 10 000 women aged 45-49. Factors increasing risk: Past thromboembolic events, hypertension, cigarette smoking, hyperlipidemia, diabetes, and obesity. The guidelines recommend identifying such risk factors, and increased efforts to modify risk factors in women taking contraceptives.

E. Menopause and Hormonal Replacement:

Use of hormone therapy in post-menopausal women is a unique risk factor for stroke. Many gaps remain in research about the magnitude of harms and risks.

F. Depression and Psychological Stress:

Several studies have indentified depression and psychological stress as factors that might increase risk of incident stroke in women by 25% to 45%. Studies including men have also reported increased risk. It is difficult to state that women are at greater risk.

STROKE PREVENTION STRATEGIES

A. Healthy lifestyle:

The guidelines recommend maintaining a healthy weight, a healthy diet, absence from smoking, regular physical exercise, moderate alcohol, and achieving normal BP, cholesterol, and blood glucose. Several high-risk factors for stroke include obesity, physical inactivity, and the metabolic syndrome. But few data suggest that these conditions increase risk disproportionally in women.

However, a recent meta-analysis found that diabetic women had a 27% greater relative risk of stroke than diabetic men. The mechanism is not known. It may be related to a more adverse cardiovascular risk profile in diabetic women.

B. Carotid Stenosis:

Women with recent stroke or TIA ipsilateral to the stenosis may be less likely to receive endarterectomy than men. The guideline recommendation is the same for both sexes.

C. Aspirin for Stroke Prevention:

There is no convincing evidence that any particular anti-platelet therapy or dosage of such therapy is more or less beneficial in women than in men.

The guideline suggests considering aspirin in women older than 65 if BP is controlled and the benefit of preventing ischemic stroke and myocardial infarction outweighs the risk of gi bleeding and hemorrhagic stroke.

NEW RECOMMENDATIONS

A. Pregnancy and Pregnancy Complications:

Risk of stroke in pregnancy is low (about 34 for 100 000 deliveries). The risk is highest in the postpartum period. (Up to 12 weeks after birth.) Suspicion for a post-partum stroke should be heightened in women who develop new-onset headache, blurred vision, or seizures or any new neurological sign during the postpartum period.

B, Pregnancy and Eclampsia:

Eclampsia occurs in about 5% of pregnancies. It is defined as high BP in pregnancy associated with proteinuria (> 300 mg/24 hours) or thrombocytopenia, impaired liver function, progressive renal insufficiency, pulmonary edema, or new onset of cerebral visual disturbance. The definition of preeclampsia has recently been changed to include women without proteinuria if one of the other features is present.

A history of preeclampsia is associated with a 2-fold risk for stroke and a 4-fold risk for hypertension later in life.

C. Moderate Hypertension of Pregnancy:

Consider treating women with systolic between 150-159 or diastolic between 100 and 109 of new onset during pregnancy. Treatment reduces risk of severe hypertension.

CCONCLUSION

This guideline provides recommendations for prevention of stroke in women, emphasizing risks that are unique or more prevalent in women. Many gaps in the literature remain.

Annals Internal Medicine June 17, 2014; 160:853-56
Guideline By the AHA/ASA, first author Cheryl Bushnell, Wake Forest Baptist Medical Center, Winston-Salem. NC

An article in Lancet June 7.2014;383:1973-80 adds diabetes to the list of risk factors: "Diabetes as a Risk Factor for Stroke in Women Compared with Men: Systematic review and meta-analysis of 64 cohorts including 775 385 individuals and 12 539 strokes" First author Sanne A E Peters, University Medical Center, Utrecht, Netherlands

Diabetes is a major cause of death and disability and is a strong factor for stroke. Whether it is a stronger risk factor for women than for men is not known.

This study was based on studies published between 1966 and 2013. All reported sex-specific estimates of relative risks of stroke (fatal and non-fatal) associated with diabetes.

The relative risk (RR) of stroke associated with diabetes (vs no diabetes) was 2.28 for women and 1.83 for men. Compared with men with diabetes, women with diabetes had a RR of stroke of 1.27 (27% greater). This was independent of other major cardiovascular risk factors.

The authors comment: Data from recent studies suggest that, even when treated similarly, women are less likely to achieve target values for systolic BP, LDL-cholesterol, fasting blood glucose, and HbA1c. The diabetes-related excess risk of stroke in women may be due to their having a chronically raised cardiovascular risk profile in the pre-diabetic state, which is more likely to go undetected and therefore untreated than in men, rather than by any substantial sex difference in the effects and complications of diabetes per se.

This meta-analysis provides the most definitive and convincing evidence so far of a sex difference in diabetes-related risk of stroke.

The CHAD2 Score is a clinical prediction rule for estimating the risk of stroke in patients with non-rheumatic AF.

It consists of 5 risk markers:

- *Congestive heart failure*
- *Hypertension (over 140/90*
- *Age over 75*
- *Diabetes*
- *Stroke or TIA of thromboembolism*

One point is given for each factor, except for the last, which receives 2 points.

- *A score of zero indicated low risk. Recommended treatment is none or aspirin. For a score of 1, aspirin or oral anticoagulants*
- *For any score 2 or above, anticoagulation.*

The CHAD2DS-VASc score adds 1 point for vascular disease, 2 points for age over 75, and 1 point for female sex.

==========

6-4 ASSOCIATION OF BARIATRIC SURGERY (BS) WITH LONG-TERM REMISSION OF TYPE-2 DIABETES AND WITH MICROVASCULAR AND MACROVASCULAR COMPLICATIONS: Prospective Matched Cohort Study

Type-2 diabetes (DM-2) is preventable. The incidence of DM-2 can be reduced by as much as 50% by lifestyle and pharmacological interventions.

In a previous Swedish Obesity Subjects (SOS) study, BS reduced the long-term incidence of DM-2 by about 80%.

Remission from established DM-2 is less common following life-style interventions, exercise alone, weight loss medication, or antidiabetic drug treatment. Lifestyle interventions and pharmacotherapy do not reduce the incidence of cardiovascular events (CVE) in obese individuals with DM-2 or other high-risk groups with increased body weight. In contrast, short-term DM-2 remission after BS occurs in 60% to 90% of patients.

The principal aims of this study were to determine diabetes remission rates following BS as compared with usual care after a mean follow-up of 10 years and the association of BS with microvascular and macrovascular diabetes complications after a mean follow-up of 18 years.

STUDY

1. Participants were 343 individuals who chose to undergo BS and a matched cohort of 260 controls. Inclusion criteria: Age 37 to 60; body mass index 34 or more in men and 38 or more in women. All were acceptable surgical risks. All had DM-2 at baseline.
2. Primary outcome = diabetes remission, relapse, and incidence of diabetes complications.
3. Patients in the control group received the customary treatment for obesity and diabetes at their primary care centers. Both groups were followed frequently for 15 years.
4. DM-2 was defined by a fasting plasma glucose 126 mg/dL or higher, or use of medications for diabetes.
5. Diabetes remission was defined as blood glucose lower than 110 mg/dL and no diabetes medication. Patients with remission could either have impaired fasting glucose (90 to <110 mg/dL) or normal fasting blood glucose (< 90).
6. Diabetes complications:
   Microvascular diabetes complications:
   Cumulative incidence of eye, kidney, and peripheral nerve complications, whichever came first.
   Macrovascular:
   Cumulative incidence of legs, heart, and brain complications, whichever came first.
7. For cumulative incidence of micro-and macro-vascular complications, the time interval was calculated between the start of the intervention and death or first hospitalization for diagnosis or treatment.

RESULTS:

1. Entered particpants between 1987 and 2001. The current analysis included 260 controls and 343 surgery patients (banding, or gastric bypass).
2. Median follow-up = 10 years for diabetes assessment and 17.6 years for diabetes complications.

3. Baseline characteristics:	Controls (n = 260)	BS Study group (n = 343)
Men	40%	41%
Age (mean)	50	49
Weight (mean; pounds)	242	271
Body mass index	40	42

Fasting glucose (mean)	156	156
Insulin treatment (%)	13	12
Oral diabetes drugs (%)	39	35
Diabetes duration (years)	3.3	2.9

4. Changes over time (pounds; mean)

2-year weight change	-6.6 (-8%)	-57.8 (-14%)
10-year weight change	-9.6 (-12%)	-50.3 (-15%)
No. of patients at 10 years	134	230

5. Diabetes remissions (%)

	Control	BS group
2 years	16	72
10 years	10*	38
15 years	6*	30

* My estimates from figure 1

6. Diabetes remission and relapse in the BS group:

A short duration of diabetes at baseline was associated with a higher diabetes remission rate in surgery patients after 2, 10, and 15 years. Baseline BMI was not associated with diabetes remission or relapse.

Remissions (FBG less than110) by diabetes duration in the surgery group;

Percentage (%) without diabetes during follow-up:

Duration	2 years	10 years	15 years
< 1 year	96	60	46
1-3 years	68	24	12
4 and over	39	10	6

7. BS and diabetes complications:

BS was associated with decreased incidence of vascular complications:

Incidence rate per 1000 person-years:

	Microvascular	Macrovascular
Controls	41	44
Surgery	21	32
Hazard ratio surgery /controls	0.44	0.68

8. Longer diabetes duration at baseline (15 years vs 1 year) was associated with lower benefit in reduction of vascular complications

DISCUSSION

1. DM-2 has traditionally been considered a chronic disease, and typically less than 15% of treated patients achieve remission through non-surgical means.
2. In this report,72% of surgically treated patients were in remission at 2 years, while 16% had remitted in the control group.
3. There was an excellent 2-year remission rate in this surgery group, but only 38% and 30% were still in remission at 10 and 15 years.
4. Remission rates are typically higher after gastric bypass than after banding.
5. Tight glycemic controls by drug treatment may reduce the incidence of microvascular disease, but

tight control is seldom achieved in obese diabetics, and lifestyle changes and drug therapy have not typically reduced the incidence of macrovascular diseases. These investigators recently demonstrated that BS was associated with a reduced 20-year incidence of myocardial infarction, not only in obese patients in general, but also in obese patients with diabetes. Recently, a favorable 5-year effect of BS on albuminuria has been reported.

6. Short diabetes duration at baseline is associated with more factorable short-term diabetes remission at 10 to 15 years after BS, and with greater prevention of diabetic complications for up to 25 years.
7. The diagnosis of diabetes in this study was based on fasting glucose levels and self-reported use of diabetes medication. Using the glucose tolerance test and HbA1c might have changed the results to some extent.

CONCLUSION

In this very long-term follow-up observational study of patients with diabetes, BS was associated with more frequent diabetes remissions and fewer complications than usual care.

JAMA June 1, 2014;311:2292-30 doi:10.1001/jama.2014.5988
Original investigation, first author Lars Sjostrom. Sahlgrenska University Hospital, Gothenburg, Sweden

---

This is an interesting and important study. The diabetic state can be reversed. When the diabetes is remitted, micro- and macrovascular complications are reduced.

Can we say that patients in remission were cured of their diabetes? I think not. Their propensity to regain diabetes status remains. Between years 2 and 10, over half of the BS patients who had lost their diabetes state regained it.

Why should a short duration of diabetes at baseline be associated with greater remission rates from surgery? And with greater prevention of diabetic complications? The investigators did not comment.

There was considerable loss of participants over 10 or more years.

6-5 ASSOCIATION OF AZITHROMYCIN WITH MORTALITY AND CADIOVASCULAR EVENTS AMONG OLDER PATIENTS HOSPITALIZED FOR PNEUMONIA: Population-based retrospective cohort study

Pneumonia and influenza together are the leading causes of infection-related death in the USA.

The Infectious Disease Society of America has published guidelines for community-acquired pneumonia, which recommends the use of macrolides as part of combination antibiotic therapy for patients hospitalized with community-acquired pneumonia.

There is little randomized clinical evidence for this.

However, there is some evidence that azithromycin is associated with QT prolongation and cardiac arrhythmias.

Further research is required to examine the safety of azithromycin in patients hospitalized with community-acquired pneumonia.

This study aimed to assess the association of azithromycin use and outcomes within 90 days of hospital admission, including CVD events (myocardial infarction (MI), heart failure, cardiac arrhythmias) and mortality for patients 65 years and older hospitalized with pneumonia.

STUDU

1. Population-based cohort study used data from the VA health system (150 hospitals and 850 outpatient clinics). All subjects were hospitalized between 1991-2012.
2. Patients were included if they were age 65 or older, were hospitalized with pneumonia, and received antibiotic therapy concordant with national clinical practice guidelines.
3. All had at least 3 VA outpatient visits in the year preceding to ensure appropriate assessment of co-morbidities.
4. All received antibiotic consistent with current guidelines.
5. Excluded patients who received a macrolide other than azithromycin or doxycycline because of the small number of recipients.
6. Classified patients as having used azithromycin if they had received at least 1 dose during the first 48 hours.
7. Examined the association of azithromycin and other guideline-concordant antibiotics with all-cause mortality and cardiovascular events in patients hospitalized with pneumonia.
8. Outcomes included 30- and 90-day all-cause mortality and 90-day cardiac arrhythmias, heart failure, MI, and any other cardiac event.

RESIULTS

1. 31 863 patients were exposed to azithromycin and 31 863 propensity-matched patients received other guideline-concordant antibiotics. After matching, there was no significant difference in potential confounders between groups
2. Ninety day mortality was significantly lower in those who received azithromycin vs those receiving other antibiotics (17% vs 22%; odds ratio 0.73)
3. However, there were significant increased odds of MI in the azithromycin group (5.1% vs 4.4%; odds ratio 1.17) but not any cardiac event (OR 0.99), cardiac arrhythmia (OR 0.99) or heart failure (OR 1.01)

DUSCUSSION

1. Azithromycin was consistently associated with decreased mortality and slightly increased odds of MI. This supports the current guidelines for community-acquired pneumonia that recommend azithromycin as part of combination therapy for patients hospitalized with pneumonia.
2. The number needed to treat with azithromycin to prevent one death within 90 days was 21. The number needed to harm from MI was 144.
3. A previous study reported that azithromycin use, compared with non-antibiotic use was associated with an increased risk of MI (HR = 2.88) and an increase in risk of cardiovascular death (HR = 2.49).
4. Azithromycin can cause QT prolongation, which may lead to cardiac arrhythmias. But it is considered the safest of all macrolide antibiotics from a cardiac standpoint.
5. Numerous studies have demonstrated that combination therapy with a beta-lactam plus

a macrolide is superior to beta-lactam-only therapy in community-acquired pneumonia.

6. Other observational studies of pneumonia suggest that combination antibiotic therapies with macrolides have outcomes superior to fluoroquinolones alone or other combination therapy including fluoroquinolones.

CONCLUSION

Among older patients hospitalized with pneumonia, treatment that included azithromycin compared with other antibiotics was associated with a lower risk of 90-day mortality. There was a small increase in cardiac events, including MI.

JAMA June 4, 2014; 311: 2199-2208 doi:10.1001/jama.2014.4304
First author Eric M Mortensen, VA Medical Center, Dallas Texas

---

Macrolides are so named because of the presence of a macrolide carbon ring in the center of the molecule.

The FDA has approved 4 antibiotic macrolides: Azithromycin (unique. It does not inhibit CYP3A4); clarithromycin; eruthromycin; and telithromycin.

They are used to treat infections caused by Gram-positive bacteria (eg. Streptococcus pneumonia) and Hemophiles influenza.

Their antimicrobial spectrum is slightly wider than that of penicillin. Unlike penicillin, they have efficacy against Legionella pneumophilia, mycoplasma, mycobacteria, some rickettsia, and chlamydia.

Beta-lactams are named after the beta-lactam carbon ring in the center of the molecule. They are now in their 5th generation. There are many. Many are broad spectrum.

Names familiar to me include: penicillin; cloxacillin; dicloxacillin; carbenicillin; ticarcillin; cephixitin; cephaoosporin.

Source: Wikipedia