

Metformin-induced lactic acidosis extremely rare

Salpeter SR, Greyber E, Pasternak GA, Salpeter EE. Risk of fatal and nonfatal lactic acidosis with metformin use in type 2 diabetes mellitus. *Arch Intern Med* 2003; 163:2594–2602.

■ CLINICAL QUESTION

What is the risk of lactic acidosis accompanying metformin therapy for patients with type 2 diabetes?

■ BOTTOM LINE

The link between metformin and lactic acidosis, when used as prescribed, is tenuous. The bigger question is whether lactic acidosis risk truly increases when we relax criteria and give it to patients previously forbidden to take it. (LOE=1a)

■ STUDY DESIGN

Systematic review

■ SETTING

Outpatient (any)

■ SYNOPSIS

It's tricky to try to prove the nonexistence of a phenomenon. The adage holds: Absence of proof is not proof of absence. So, how much absence of proof do we need?

The authors of this study combined the results of all randomized controlled trials and observational studies to determine the risk of lactic acidosis with metformin. The literature search was thorough and included unpublished data. Two independent reviewers evaluated articles for inclusion. The methodologic quality of the studies was evaluated using modified quality criteria. Of the 194 studies in the analysis,

126 were randomized controlled studies and 68 were observational research. More than 18,000 participants in these studies received metformin for an average 2.1 years (36,893 patient-years).

There were no cases of lactic acidosis in the metformin-treated group or in the comparison group. Not surprising, since patients with risk factors for lactic acidosis were undoubtedly not enrolled in any of the studies, and monitoring was more intense than in typical practice. Population studies estimate the rate of lactic acidosis to be between 2 and 9 cases per 100,000 patient-years (which is also the rate of lactic acidosis in patients with diabetes not receiving metformin). Using these numbers, 1 to 3 cases of lactic acidosis would have been expected. Several studies evaluated lactic acid levels in metformin-treated patients, finding no difference in baseline lactic acid levels compared with those not treated with metformin.

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Ximelagatran effective in preventing stroke in a nonvalvular atrial fibrillation

Executive Steering Committee on behalf of the SPORTIF III Investigators. Stroke prevention with the oral direct thrombin inhibitor ximelagatran compared with warfarin in patients with non-valvular atrial fibrillation (SPORTIF III): randomised controlled trial. Lancet 2003; 362:1691-1698.

■ CLINICAL QUESTION

Is ximelagatran as effective as warfarin in preventing stroke for patients with nonvalvular atrial fibrillation?

■ BOTTOM LINE

In this manufacturer-sponsored, open-label study, patients with atrial fibrillation and at increased risk for stroke treated with either ximelagatran or warfarin have comparable outcomes. If these results are confirmed independently, ximelagatran may become the preferred treatment, since it doesn't require monitoring and may cause fewer bleeding complications. (LOE=2b).

■ STUDY DESIGN

Randomized controlled trial (nonblinded)

■ SETTING

Other

■ SYNOPSIS

Patients with atrial fibrillation were recruited from hospitals, doctor's offices, and health-care clinics to participate in this manufacturer-sponsored open-label study comparing fixed doses of ximelagatran (n=1704) with warfarin dosed to maintain an international normalized ratio (INR) between 2.0 and 3.0 (n=1703). Patients also needed to have at least 1 additional stroke risk factor to be included: hypertension, age older than 75 years, previous thromboembolic phenomena, left ventricular ejection fraction less than 40%, symptomatic congestive heart failure, or age older than 65 years with coronary

artery disease or diabetes mellitus.

There were a large number of exclusion criteria, including recent stroke, transient ischemic attack, acute coronary syndrome, conditions associated with increased bleeding risk, endocarditis, planned major surgery, and cardioversion. Allocation to treatment group was masked.

The primary outcome, all stroke (ischemic or hemorrhagic) and systemic embolic events, was assessed via intention to treat. The secondary endpoints, also assessed by intention to treat, included bleeding; treatment discontinuation; ischemic stroke, transient ischemic attack, systemic embolism; and death, stroke, systemic embolism, and acute myocardial infarction. The study was designed to have 90% power, a minimum of 12 months of follow-up per patient, and an aggregate of 80 primary events. The main outcomes were assessed by local study-affiliated neurologists or stroke specialists, masked to treatment. The researchers had data on all but 10 patients, who never took the study drug. Slightly more patients taking warfarin completed the study (86% vs 82% taking ximelagatran).

The total mortality was approximately the same in each group (4.6%). The mean length of follow-up was 17 months. In the group treated with warfarin, 56 patients had primary events during 2440 patient-years (yearly rate=2.3%) compared with 40 patients in the ximelagatran group during 2446 patient-years (yearly rate=1.6%). This difference was not significant. The rate of secondary events in each group was similar, with the exception of bleeding complications. These occurred less often in the ximelagatran group (26% per year) than in the warfarin group (30% per year).

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CONTINUED

Hyaluronic acid minimally effective for knee osteoarthritis

Lo GH, LaValley M, McAlindon T, Felson DT. Intra-articular hyaluronic acid in treatment of knee osteoarthritis: a meta-analysis. *JAMA* 2003; 290:3115-3121.

■ CLINICAL QUESTION

Is intra-articular hyaluronic acid effective in the treatment of knee osteoarthritis?

■ BOTTOM LINE

Intra-articular hyaluronic acid (Provisc, Synvisc, Suplasyn) is minimally, if at all, more effective than placebo in the treatment of knee osteoarthritis. The evidence of publication bias against negative trials in this meta-analysis suggests that any overall positive effect is overestimated. The highest-molecular-weight hyaluronic acid (Synvisc) may be more effective than lower-molecular-weight hyaluronic acid. (LOE=1a-)

■ STUDY DESIGN

Meta-analysis (randomized controlled trials)

■ SETTING

Various (meta-analysis)

■ SYNOPSIS

Intra-articular hyaluronic acid for knee osteoarthritis is an expensive therapy that has been widely used since US Food and Drug Administration approval in 1997. The efficacy of this procedure remains, however, controversial.

Two independent researchers performed an extensive search for both English-language and non-English-language studies on MEDLINE and the Cochrane Controlled Trials Register, and in manuscript bibliographies and abstracts from scientific meetings. They also attempted to include unpublished studies by contacting all authors to ask if they knew of any further trials. Only randomized trials with a minimum follow-up time of 2 months and dropout rate of less

than 50% were included. Intention-to-treat analyses were used whenever possible.

From a total of 57 initial studies identified, 22 met the inclusion criteria. The overall dropout rate of these trials was 12.4%. In almost all the trials the 95% confidence intervals included an effect size of zero, consistent with no effect of the treatment.

Two trials, both evaluating the highest-molecular-weight hyaluronic acid, found the greatest benefit of treatment and were thus heterogeneous (outliers) with the remaining studies. Analysis using a number of statistical tests, including a funnel plot and an Egger test, found evidence of publication bias against negative trials.

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Annual proteinuria screening not cost-effective

Boulware LE, Jaar BG, Tarver-Carr ME, Brancati FL, Powe NR. Screening for proteinuria in US adults. A cost-effective analysis. *JAMA* 2003; 290:3101-3114.

■ CLINICAL QUESTION

Is annual proteinuria screening in adults cost-effective?

■ BOTTOM LINE

Annual screening of adults to detect proteinuria and prevent end-stage renal disease (ESRD) is not cost-effective unless directed only at high-risk groups (that is, those patients with diabetes and hypertension). Screening every 10 years beginning at the age 60 years, however, is highly cost-effective. (LOE=1b)

■ STUDY DESIGN

Cost-effectiveness analysis

■ SETTING

Not applicable

■ SYNOPSIS

The majority of patients who develop ESRD go undetected until prevention is ineffective. The

presence of low levels of urine protein can be an early marker of increased risk of progressive kidney disease, but it is unclear whether the screening of all adults for proteinuria is indicated. Screening diabetic patients for proteinuria with an annual dipstick has already been shown to be cost-effective.

To assess the value of population-based dipstick screening for early detection of urine protein in all adults, the researchers performed a cost-effectiveness analysis using a Markov decision model to compare a strategy of screening with no screening beginning at age 50 years. Patients identified with proteinuria began treatment with either an angiotensin-converting enzyme inhibitor or an angiotensin II-receptor blocker.

The researchers did a careful analysis of the literature to obtain estimates of event probabilities (including estimated compliance rates, natural disease progression, potential harms from unnecessary interventions, and treatment benefits) and costs, including both direct and indirect costs. Sensitivity analyses were performed for age, frequency of screening, and disease risk factors. Outcomes were based on cost per quality-adjusted life-year (QALY), which is a commonly used parameter to compare various screening tests and interventions.

The cost-effectiveness of annual screening of patients aged younger than 60 years with neither hypertension nor diabetes was unfavorable (\$282,818 per QALY; gain of 0.0022 QALYs per person). Annual screening of low-risk patients aged 60 years and older was more cost-effective (\$53,372 per QALY). For patients with hypertension, annual screening was highly cost-effective (\$18,621 per QALY; gain of 0.03 QALYs per person). A lower frequency of screening low-risk patients every 10 years beginning at age 60 was also cost-effective (\$6,195 per QALY).

HPV testing may replace Pap smears for primary screening

Cuzick J, Szarewski A, Cubie H, et al. Management of women who test positive for high-risk types of human papillomavirus: the HART study. Lancet 2003; 362:1871-1876.

■ CLINICAL QUESTION

Can human papillomavirus testing replace Papanicolaou tests as the primary means of screening for cervical cancer?

■ BOTTOM LINE

Using human papillomavirus (HPV) testing is likely to replace Papanicolaou (Pap) testing for primary screening for cervical cancer for a variety of reasons—detection of the etiologic factor should predate the development of disease; urine testing for HPV may remove patient barriers to screening; and reduced interpretation error. This study can't really provide the kind of data to support this, however. It is even more likely that vaccination against HPV may render both these technologies obsolete. (LOE=2b)

■ STUDY DESIGN

Randomized controlled trial (nonblinded)

■ SETTING

Outpatient (primary care)

■ SYNOPSIS

In this multicenter screening study, 11,085 women aged 30 to 60 years were recruited from 161 family practices in the United Kingdom. To be eligible, the women could not have had an abnormal Pap result in the preceding 3 years and could never have been treated for cervical intraepithelial neoplasia (CIN). Women had a standard Pap test using an extended-tip Ayre's spatula and a sample was placed into transport medium. Women with mild dyskaryosis or worse were referred for colposcopy.

A total of 825 women (8%) showed minimal

CONTINUED

Evidence-based medicine ratings

THE JOURNAL OF FAMILY PRACTICE uses a simplified rating system system called the Strength of Recommendation Taxonomy (SORT). More detailed information can be found in the February 2003 issue, "Simplifying the language of patient care," pages 111–120.

Strength of Recommendation (SOR) ratings are given for key recommendations for readers. SORs should be based on the highest-quality evidence available.

- A Recommendation based on consistent and good-quality patient-oriented evidence.
- B Recommendation based on inconsistent or limited-quality patient-oriented evidence.
- C Recommendation based on consensus, usual practice, opinion, disease-oriented evidence, or case series for studies of diagnosis, treatment, prevention, or screening

Levels of evidence determine whether a study measuring patient-oriented outcomes is of good or limited quality, and whether the results are consistent or inconsistent between studies.

STUDY QUALITY

- 1—Good-quality, patient-oriented evidence (eg, validated clinical decision rules, systematic reviews and meta-analyses of randomized controlled trials [RCTs] with consistent results, high-quality RCTs, or diagnostic cohort studies)
- 2—Lower-quality patient-oriented evidence (eg, unvalidated clinical decision rules, lower-quality clinical trials, retrospective cohort studies, case control studies, case series)
- 3—Other evidence (eg, consensus guidelines, usual practice, opinion, case series for studies of diagnosis, treatment, prevention, or screening)

Consistency across studies

Consistent—Most studies found similar or at least coherent conclusions (coherence means that differences are explainable); or If high-quality and up-to-date systematic reviews or meta-analyses exist, they support the recommendation

Inconsistent—Considerable variation among study findings and lack of coherence; or If high-quality and up-to-date systematic reviews or meta-analyses exist, they do not find consistent evidence in favor of the recommendation

abnormalities (borderline cytology, or positive high-risk HPV test results and negative cytology) and were randomized to immediate colposcopy or surveillance by HPV testing and cytology at 6 and 12 months. Women in the surveillance group were referred for colposcopy at 6 months if the cytology result progressed to mild dyskaryosis or worse. In all other cases the women were invited for colposcopy and repeat testing at 12 months. HPV testing was more sensitive than abnormal Pap results (97% vs 77%; $P=.002$) at detecting CIN 2 or worse, but it was less specific (93% vs 96%; $P<.0001$).

Among the 825 randomized women, immediate colposcopy and surveillance were comparable: 45% of the surveillance women tested positive for HPV at baseline, had negative cytology, and 35% with borderline cytology were HPV negative at 6 to 12 months. None had CIN 2 or worse.

Technically speaking, this is not a trial comparing screening modalities, but rather a trial of different modes of follow-up. Since we don't have outcomes data, and since cervical cancer is relatively rare and tends to be slow-growing, these data need confirmation in larger, longer, more rigorous trials.

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DRUG BRAND NAMES

Hyaluronic acid	Hyalgan, Provisc, Synvisc, Suplasyn
Metformin	Glucophage, Glycon
Warfarin	Coumadin
Ximelagatran	Exantra

CORRECTION

In the February 2004 Language of Evidence, the equations for calculating relative risks and odds ratios were printed incorrectly. They appear corrected below.

Relative Risk =

$$\frac{\text{Incidence of disease among those exposed (a/a+b) } 355/(355+3140)}{\text{Incidence of disease among those not exposed (c/c+d) } 140/(140+2507)} = 1.92$$

Odds Ratio =

$$\frac{\text{Odds of people with disease being exposed (a/c) } 355/140}{\text{Odds of people without disease being exposed (b/d) } 3140/2507} = 2.02$$