# Impact of autologous blood injections in treatment of mid-portion Achilles tendinopathy: double blind randomised controlled trial

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**STUDY QUESTION** Do peritendinous autologous blood injections improve pain and function in people with mid-portion Achilles tendinopathy?

### SUMMARY ANSWER

The administration of two unguided peritendinous autologous blood injections one month apart, in addition to a standardised eccentric training programme, provides no additional benefit in the treatment of mid-portion Achilles tendinopathy.

### WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Several studies have suggested that injection of autologous blood can help in the treatment of various tendinopathies. There is a lack of high quality evidence showing relevant benefit for autologous blood injections, particularly in the management of mid-portion Achilles tendinopathy. We found no additional reduction in pain or improvement in function when these injections were combined with an eccentric calf training programme.

### Design

This study was a single centre, participant and single assessor blinded, parallel group, randomised controlled trial with sealed envelope allocation. Both groups carried out a standardised daily eccentric calf training programme and underwent two unguided peritendinous injections around the site of maximal Achilles tendon tenderness one month apart according to a standardised protocol, with the treatment group having 3 mL of blood injected and the control group having no substance injected. No local anaesthetic was used.

### **Participants and setting**

53 adult participants (mean age 49, 53% male) with at least three months of unilateral mid-portion Achilles tendinopathy symptoms participated in this study at a single

Absolute mean VISA-A scores over time after peritendinous autologous blood injections (treatment) or dry needling (control) 100 VISA-A score 80 60 40 20 Treatment • - Control 0<sub>Baseline</sub> 1 2 3 6 Month of follow-up sports medicine clinic. Participants had not undergone any previous adjuvant therapies such as corticosteroid or sclerosant injections, prolotherapy, glyceryl trinitrate patches, or extracorporeal shockwave therapy.

### **Primary outcomes**

The primary outcome measure was the change in symptoms and function from baseline to six months according to the validated Victorian Institute of Sport Assessment-Achilles (VISA-A) score. Secondary outcomes were the participant's perceived rehabilitation measured with a Likert score and their ability to return to sport.

### Main results and the role of chance

26 participants were randomly assigned to the treatment group and 27 to the control group. 50 (94%) completed the six month study, with 25 in each group. Clear and clinically worthwhile improvements in the VISA-A score were evident at six months in both the treatment (18.7, 95% confidence interval 12.3 to 25.1) and control (19.9, 13.6 to 26.2) groups. The overall effect of treatment, however, was not significant (P=0.689) and the 95% confidence intervals at one, two, and three month follow-up points precluded any clinically meaningful benefit or harm. There was no significant difference between groups in regards to their perceived rehabilitation or ability to return to sport or their compliance with the eccentric calf strengthening programme.

### Harms

No adverse events were reported.

# Bias, confounding, and other reasons for caution

This study did not use ultrasound guidance, which could be used in some settings.

# Generalisability to other populations

The study participants reflected a wide range of New Zealand society with ages ranging from 27 to 76 and sex being evenly matched with 53% men and 47% women. The mean length of symptoms among participants was 31 months, with 92% normally being physically active or involved in sport. There was an under-representation of minority ethnic groups, with 91% of the participants identifying themselves as European and 9% as New Zealand Maori.

### **Study funding**

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

### **Trial registration**

ACTRN12610000824066

# Effect of dutasteride on clinical progression of benign prostatic hyperplasia in asymptomatic men with enlarged prostate: a post hoc analysis of the REDUCE study

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### **STUDY QUESTION**

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Is there a role for dutasteride in preventing clinical progression of benign prostatic hyperplasia among asymptomatic men with an enlarged prostate?

### SUMMARY ANSWER

In this post hoc analysis dutasteride significantly decreased the incidence of progression of benign prostatic hyperplasia.

### WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Men with an enlarged prostate are at risk of urinary symptoms and complications, but no major trial of dutasteride (an established treatment for lower urinary tract symptoms due to benign prostatic hyperplasia) has included asymptomatic or minimally symptomatic men. This study uniquely estimates the benefit of dutasteride among men with no or minimal symptoms at risk of complications due to prostate enlargement.

### **Participants and setting**

Participants in the Reduction by Dutasteride of Prostate Cancer Events (REDUCE) study with a previous negative biopsy for prostate cancer were randomised in a double blind fashion to placebo or dutasteride and followed over four years. We examined data for all men in the REDUCE study with a prostate size >40 mL and a baseline International Prostate Symptom Score (IPSS) <8 (mild or no urinary tract symptoms). We excluded subjects who took medications for benign prostatic hyperplasia at study entry.

### Design, size, and duration

We compared the risk of clinical progression of benign prostatic hyperplasia at four years between both arms. Our cohort consisted of 825 men who took placebo, and 792 who took dutasteride. Clinical progression of benign prostatic hyperplasia was defined as a  $\geq$ 4 point worsening on IPSS, acute urinary retention related to benign prostatic hyperplasia, urinary tract infection, or surgery related to benign prostatic hyperplasia.

### Main results and the role of chance

A total of 464 men (29%) experienced clinical progression of benign prostatic hyperplasia at four years: 297 (36%) who took placebo, 167 (21%) who took dutasteride (P<0.001). The relative risk reduction associated with dutasteride use was 41%, and the absolute risk reduction was 15%, with a number needed to treat (NNT) of 6.7. Among men who had acute urinary retention and surgery related to benign prostatic hyperplasia, the absolute risk reduction for dutasteride was 6.0% and 3.8%, respectively. On multivariable regression analysis adjusting for covari-



Absolute rates and relative risk reduction for events



AUR=acute urinary retention. BPH=benign prostatic hyperplasia. RRR=relative risk reduction.

ates, dutasteride significantly reduced benign prostatic hyperplasia clinical progression with an odds ratio of 0.47 (95% CI 0.37 to 0.59, P<0.001). Analysis of time to first event yielded a hazard ratio of 0.673 (P<0.001) for those who took dutasteride.

### Bias, confounding, and other reasons for caution

The groups were well balanced for all baseline factors in this well conducted multicentre trial. While this post hoc analysis suggests that dutasteride is effective in this population, there remains a need to weigh the benefits against harms for each patient. This study presents unique data from which to do this. The trade-offs to the patient are the side effects and cost. Adverse events were similar to previous reports, with sexual adverse events most common.

### Generalisability to other populations

The REDUCE study includes men with a previous negative prostate biopsy, and the population is enriched with men with benign prostatic hyperplasia. Men with a prostate size >80 mL were excluded from the original study. Our study estimates the benefit of dutasteride in men with an enlarged prostate who are asymptomatic, providing key information for physicians and policy makers.

# Study funding/potential competing interests

AF, NF, and AZ have received research grants and honorariums from GlaxoSmithKline; NF and AF do consultancy for GlaxoSmithKline and Merck.

# **bmj.com O** Diabetes updates from BMJ Group are at bmj.com/specialties/diabetes

# Comparative safety and effectiveness of sitagliptin in patients with type 2 diabetes: retrospective population based cohort study

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### **STUDY QUESTION**

Is the use of sitagliptin in newly treated patients with type 2 diabetes associated with any changes in all cause hospital admission or all cause mortality?

### SUMMARY ANSWER

Sitagliptin was not associated with any appreciable excess risk of all cause hospital admission or all cause mortality in a broad spectrum of patients with newly treated diabetes or in higher risk groups such as patients with a history of ischaemic heart disease or with reduced kidney function.

### WHAT IS KNOWN AND WHAT THIS PAPER ADDS

No large published studies have evaluated the effect of sitagliptin on broad outcomes such as all cause hospital admissions or mortality in "real world" patients. Our observational data provide evidence of the comparative safety of sitagliptin and support current recommendations to use sitagliptin as add-on therapy if needed in people with diabetes.

# **Participants and setting**

We followed an inception cohort of new users of oral antidiabetic drugs between 2004 and 2009 until death, termination of medical insurance, or 31 December 2010.

# Design, size, and duration

We did a population based retrospective cohort study using a large US claims and integrated laboratory database that included employed, commercially insured patients with dependants from all 50 states. Using time varying Cox proportional hazards regression, we compared the risk of all cause hospital admission and all cause mortality (primary endpoint) and the combined endpoint of cardiovascular related hospital admissions or all cause mortality, all cause mortality, all cause hospital admissions, and cardiovascular related hospital admissions (secondary endpoints) for patients using sitagliptin and those not using sitagliptin after adjustment for demographics, clinical and laboratory data, pharmacy claims data, healthcare use, and time varying propensity scores.

#### Main results and the role of chance

Our cohort included 72 738 new users of oral antidiabetic drugs (8032 (11%) used sitagliptin). The average age was 52 (SD 9) years, 54% (39 573) were men, 11% (8111) had ischaemic heart disease, and 9% (6378) had diabetes related complications at the time their first antidiabetic drug was prescribed. All cause hospital admission or death occurred in 14 215 (20%) patients; sitagliptin users had similar rates to patients not using sitagliptin (adjusted hazard ratio 0.98, 95% confidence interval 0.91 to 1.06).

We found similar results in patients with a history of ischaemic heart disease or with an estimated glomerular filtration rate below 60 mL/min. Furthermore, we found no difference in the combined endpoint of cardiovascular related hospital admissions or mortality, all cause mortality, all cause hospital admissions, and cardiovascular related hospital admissions. We also found no association between the use of sitagliptin and the risk of acute pancreatitis or the risk of acute upper respiratory tract infections.

### Bias, confounding, and other reasons for caution

Although we were able to use detailed clinical data and a strong analytical design, this is an observational study. Our results may be attributed to selection bias in that physicians may have given or withheld sitagliptin in patients perceived to be at varying degrees of risk. Moreover, we were not able to adjust fully for unmeasured confounders such as blood pressure or body weight.

# Generalisability to other populations

Our population largely consisted of middle aged patients with commercial health insurance.

# Study funding/potential competing interests

This work was funded by operating grants from the Canadian Diabetes Association and the Canadian Institutes of Health Research (CIHR). DTE receives salary support from Alberta Innovates Health Solution (AIHS) and the CIHR. FAM is a senior health scholar with AIHS.

# Adusted hazard ratios for outcome of all cause hospital admission and all cause deathaccording to sitagliptin exposure

Any sitagliptin use

Any sitagliptin use in patients with history of IHD Any sitagliptin use in patients with eGFR <60 mL/min High dimensional propensity score



eGFR=estimated glomerular filtration rate; IHD=ischaemic heart disease

# Influence of trial sample size on treatment effect estimates: meta-epidemiological study

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Does trial sample size, and not only small trials, influence treatment effect estimates within meta-analyses?

# SUMMARY ANSWER

Treatment effect estimates differ within meta-analyses solely based on trial sample size, with stronger estimates seen in small to moderately sized trials than in the largest trials.

### WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Our knowledge about the influence of trial sample size on treatment effect estimates is based on the small study effect: the tendency for small trials (rather than large trials) to report large treatment benefits within one meta-analysis. We found significantly larger estimates of treatment effect in smaller trials regardless of sample size; estimates differed within meta-analyses solely based on trial sample size, with stronger estimates seen in small to moderately sized trials than in the largest trials.

### Selection criteria for studies

This meta-epidemiological study assessed 93 meta-analyses including 735 randomised controlled trials with binary outcomes, published in the 10 leading journals of each medical subject category of the Journal Citation Reports or in the Cochrane Database of Systematic Reviews. Trials within each meta-analysis were sorted according to their sample size, by two approaches. Firstly, trials were separated into quarters (ranging from quarter 1, which included 25% of the smallest trials, to guarter 4 including 25% of the largest trials). Secondly, trials were separated into the following size groups: fewer than 50, 50-99, 100-199, 200-499, 500-999, and 1000 or more patients. We compared treatment effects, measured as odds ratios, between the quarters and between the size groups using multilevel logistic regression models with random effects. We used  $\tau^2$  to measure the heterogeneity across meta-analyses.

### **Primary outcome**

We used ratios of odds ratios to quantify the difference in estimated treatment effect between smaller and larger trials. Average ratios of odds ratios less than 1 indicate larger treatment effects in smaller trials.

# Main results and role of chance

Treatment effect estimates were significantly larger in smaller trials, regardless of sample size. Compared with



quarter 4 (which included the largest trials), treatment effects were, on average, 32% larger in the trials in quarter 1 (which included the smallest trials; ratio of odds ratios 0.68, 95% confidence interval 0.57 to 0.82), 17% larger in trials in quarter 2 (0.83, 0.75 to 0.91), and 12% larger in trials in quarter 3 (0.88, 0.82 to 0.95). Similar results were obtained when comparing treatment effect estimates between the different size groups. Compared with trials of 1000 patients or more, treatment effects were, on average, 48% larger in trials with fewer than 50 patients (0.52, 0.41 to 0.66) and 10% larger in trials with 500-999 patients (0.90, 0.82 to 1.00).

# Bias, confounding, and other reasons for caution

To explore the influence of sample size on treatment effect, we used several complementary approaches, all showing consistent results. However, our results were based on meta-analyses of trials assessing binary outcomes; therefore, they cannot be extrapolated to trials assessing continuous outcomes, because such trials usually differ in medical condition, risk of bias, sample size, and statistical analysis.

# Study funding/potential competing interests

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