Thiazolidinedione Intervention with Vitamin D Evaluation (TIDE). A Multicenter Randomized Double-Blind Placebo-Controlled Trial of a Thiazolidinedione (TZD) or Placebo and of Vitamin D or Placebo In People With Type 2 Diabetes at Risk For Cardiovascular Disease.

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Diabetic complications
Study type	Interventional

Summary

ID

NL-OMON35554

Source
ToetsingOnline

Brief title
TIDE

Condition

- Diabetic complications

Synonym
Type 2 Diabetes

Research involving
Human

Sponsors and support

Primary sponsor: GlaxoSmithKline
Source(s) of monetary or material Support: Farmaceutische industrie

Intervention

Keyword: Cardiovacular Disease, Diabetes Type 2, Thiazolidinedione (TZD), Vitamin D

Outcome measures

Primary outcome

The composite cardiovascular primary outcome for the TZD research questions is

the first occurrence of either: a) cardiovascular death; b) nonfatal myocardial

infarction

(MI); or c) nonfatal stroke.

The composite primary outcome for the vitamin D research question is death or

serious cancer requiring hospitalization, chemotherapy or surgery.

Secondary outcome

Secondary and other outcomes to be collected:

1. all-cause mortality;

2. components of the composite outcomes;

3. a composite microvascular outcome comprising retinopathy requiring laser

therapy,

vitrectomy, a 30% decline in estimated glomerular filtration rate (GFR), or

need for

renal replacement therapy;

4. any hospitalization for heart failure,

5. any hospitalization for shortness of breath;

6. any hospitalization for pneumonia;

7. any revascularization;

8. any hospitalization for unstable, new or worsening angina;

9. any fracture;

10. any cancer;

11. other hospitalization;

12. cognitive decline equivalent to a difference of >= 1.5 units in the Digit

Symbol

Substitution Test (DSS) score;

13. erectile dysfunction (e.g. International Index of Erectile Dysfunction);

14. liver function tests;

15. quality of life (e.g. EuroQol 5D);

16. cognitive function [e.g. Montreal Cognitive Assessment (MoCA)].

Study description

Background summary

Type 2 diabetes mellitus (T2DM) is a strong, independent risk factor for cardiovascular
(CV) events and death. It is characterized by a history of hyperglycemia and reduced
metabolic effectiveness of insulin (i.e. insulin resistance), and people with T2DM as well
as those with impaired fasting glucose (IFG) and impaired glucose tolerance (IGT) have

abnormal fat distribution, renal function, lipid profiles, oxidative stress, platelet function,
and many other changes. Emerging evidence also suggests that T2DM is associated with
low vitamin D levels and a growing body of evidence links vitamin D deficiency to many
of the chronic diseases that occur in people with diabetes. Evidence has also suggested a
beneficial effect of vitamin D on the incidence of cancer. These observations suggest
that thiazolidinediones (TZDs) and/or vitamin D therapy may reduce the risk of these
diseases in high risk individuals.

Study objective

This trial will determine the relative incidence of CV outcomes compared to placebo for
the TZD class as a whole, rosiglitazone (RSG), and pioglitazone (PIO) when added to the
therapeutic regimen of a person with type 2 diabetes who has additional risk factors for
CV events. It will be powered to detect both superiority of the TZD class versus placebo,
and non-inferiority of RSG versus placebo based on a margin of 1.3 for the upper limit of
the hazard ratio*s confidence interval. Non-inferiority of RSG compared to placebo will
be assessed after approximately 4.5 years of study duration, with superiority assessments
of the TZD class conducted approximately one year later.
The trial will also separately determine whether adding vitamin D in such individuals is
superior to adding placebo with respect to reducing the incidence of death or serious
cancers requiring hospitalization, chemotherapy or surgery compared to placebo. This
will be assessed after up to 10 years of total follow-up.

Study design

This trial is a multicenter, international, randomized, double-blind, placebo-controlled
trial of the addition of a once daily TZD or placebo, and once-daily vitamin D or placebo
to the care of approximately 16,000 participants with T2DM and other CV risk

factors for
up to 5.5 years for TZDs and for up to 10 years for vitamin D. These therapies will be
tested independently using a factorial design and will be added to the regimen of
participants who will otherwise be treated according to the discretion of their physician
and/or investigator. Patients will enter a 3-week RSG and vitamin D active single-blind
run-in to assess tolerability. Once randomized, TZD study drug will be titrated.

Intervention

It will be given as 1 tablet daily containing up to 8mg of rosiglitazone or 45mg of pioglitazone
(or placebo); participants will be allocated to rosiglitazone, pioglitazone, or placebo in a
30:30:40 ratio. Vitamin D study drug will be given as one 1000IU tablet daily, or
placebo; participants will be allocated to vitamin D or placebo in a 50:50 ratio.

Study burden and risks

At the screening visit (Visit 1) after fasting 8 hours
- questions about past health (illnesses and injuries), other medications and diet.
- weight, height, blood pressure, heart rate, and waist and hip circumference will be measured.
- percent body fat may be calculated in case this procedure is applicable for the hospital.
- blood and urine will be collected.
- a pregnancy test will also be done if a woman who is capable of conceiving.

Visit 3 (randomisation visit)
- ECG,
- simple visual test
At the randomization, 2-year and final visits patient will be asked to complete questionnaires that measure your quality of life, thinking processes and erectile function (if male).

Visit 4 to 9 and yearly visits (after 1, 2, 6 months and then every 6 months)
At each visit
- questions about health, medications and any side effects.
- blood pressure, body fluid retention (edema or sudden increase in weight),

heart rate, and weight, will be made on visits 5, 6, 7, 9 and yearly visits after visit 9.
- height, and waist and hip measurements will be taken at year 1, 2 and at the end of the study.
- blood will be collected

At the 2-year (Visit 9) and final visits
- ECG
- a simple visual test
- morning urine sample
- blood drawn after 8 hours of fasting.

Side Effects Reported with Thiazolidinediones (Rosiglitazone and/or Pioglitazone)
•Fluid retention which may lead to swelling (for example ankle swelling), weight gain and rarely heart failure and difficulty breathing
•Swelling of the face, lips, mouth, tongue, or throat, which may cause difficulty in swallowing or breathing (angioedema)
•Decreased or blurred vision due to swelling (or fluid) in the back of the eye (macular edema)
•Anemia (low red blood cell count, which can cause fatigue)
•Increases in liver enzymes (which may indicate liver abnormalities)
•Modest increases in cholesterol
•Weight gain
•Low blood sugar (hypoglycemia) which may occur if a thiazolidinedione is taken with other diabetes medications
•Hives or rash (which may be itchy)
•Bone fractures especially in women and in the hand, upper arm, or foot.

Some people who have taken pioglitazone also had the following side effects:
•Erectile dysfunction
•Joint pain
•Flatulence (passing gas)

Some people who have taken rosiglitazone also had the following side effects:
•Constipation
•Increased appetite

Side effects reported with vitamin D
Some people who have taken vitamin D can have the following side effects:
•An allergic reaction (swelling of tongue, lips or throat, hives or itchy rash)
•Constipation
•Nausea, vomiting or decreased appetite
•Increased thirst and/or urination
•Muscle weakness
•Confusion

•Kidney stones

Contacts

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UNITED KINGDOM
Scientific
GlaxoSmithKline

New Frontiers Science Park
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UNITED KINGDOM

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. Men or women with: a) newly detected type 2 diabetes based on a fasting plasma glucose >= 7.0 mmol/l (126 mg/dL) or a 2 hour plasma glucose (FPG) >= 11.1 mmol/l (200 mg/dL) on an oral glucose tolerance test, or b) a history of type 2 diabetes
2. Hemoglobin A1c (A1C) 6.5-9.5% inclusive (for assays with upper limit of normal of 6%) within one month of screening
3. A) Age >= 50 years and evidence of vascular disease defined as >=1of:
a) prior myocardial infarction
b) prior stroke
c) coronary, carotid or peripheral artery revascularization >= 4 years earlier

d) previous documented myocardial ischemia on either an exercise stress test or on any cardiac imaging, or previous unstable angina with ECG changes or cardiac enzyme elevation
OR
B) Age >= 55 years and evidence of subclinical vascular disease defined as >=1 of:
a) microalbuminuria or proteinuria
b) history of treated or untreated hypertension with left ventricular hypertrophy by electrocardiogram (ECG) or echocardiogram
c) >50% stenosis on any imaging of coronary, carotid or lower extremity arteries
d) ankle/brachial index <0.9
OR
C) Age >= 60 years and at least 2 of the following cardiovascular disease risk factors:
a) current tobacco use
b) LDL-c >=3.4 mmol/L (130 mg/dL) or on a lipid lowering medication
c) HDL-c < 1.0 mmol/L (40 mg/dL) for men and < 1.3 mmol/L (50 mg/dL) for women or triglycerides >= 2.3 mmol/L (200 mg/dL)
d) BP lowering medication use or untreated SBP >= 140 mmHg or DBP >= 95 mmHg
e) Waist to hip ratio > 1.0 for men and > 0.8 for women
4. On no insulin and on <= 2 anti-diabetes drugs where at least one drug is at or below the half-maximal dose (as indicated in the MOP) with stable dosing for 10 weeks prior to screening
5. A negative pregnancy test for all females of childbearing potential (i.e., ovulating, pre-menopausal, and not surgically sterile) and agreement to use adequate birth control (according to local regulations) throughout the study
6. Adherence >= 80% and tolerability to single-blind study medication during the run-in phase
7. Provision of signed and dated informed consent prior to any study procedures

Exclusion criteria

1. Type 1 diabetes
2. Current need for insulin treatment
3. Symptomatic hyperglycemia requiring immediate therapy in the judgment of the physician
4. An acute cardiovascular event within 30 days prior to randomization
5. Symptomatic heart failure (i.e. New York Heart Association class II or higher) or any episode of previous pulmonary edema or known ejection fraction < 0.4 or current use of loop diuretics
6. Any fracture within the past 1 year
7. Currently planned coronary, carotid or peripheral artery revascularization or cardiac valve surgery
8. Coronary, carotid or peripheral artery revascularization within the 4 years prior to screening in the absence of angina, MI, or stroke in the intervening period
9. End stage renal disease requiring renal replacement therapy
10. Receiving drug therapy to treat liver disease

11. A diagnosis of cancer (other than superficial squamous, basal cell skin cancer, or adequately treated cervical carcinoma in situ) in the past 3 years or current treatment for the active cancer (other than prophylactic)
12. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) level > 2.5 times the upper limit of normal
13. A prior heart transplant or awaiting a heart transplant
14. Previous or current hypercalcemia, hyperparathyroidism, osteomalacia or other contraindication for vitamin D therapy
15. Regular use of or indication for greater than 400IU of vitamin D daily
16. Clinically or medically unstable with expected survival < 1 year
17. Unwillingness to permit sites to contact their primary physicians to communicate information about the study and the participant*s data
18. Any other factor likely to limit protocol compliance or reporting of adverse events
19. Inability to discontinue a TZD (if taking one) in the judgement of the physician/investigator
20. Contraindications to or history of hypersensitivity to the investigational products
21. History of renal stones within the past 2 years
22. Participation in another clinical trial of an investigational agent
23. Previous randomization in this study

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Other
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	06-04-2010
Enrollment:	525
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Actos
Generic name:	pioglitazone
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Avandia
Generic name:	Rosiglitazone
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	16-10-2009
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	16-12-2009
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	16-12-2009
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	16-02-2010
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	04-03-2010
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den

	Haag)
Approved WMO Date:	14-04-2010
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	18-05-2010
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	17-08-2010
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2008-005030-73-NL
ClinicalTrials.gov	NCT00879970
CCMO	NL29426.040.09