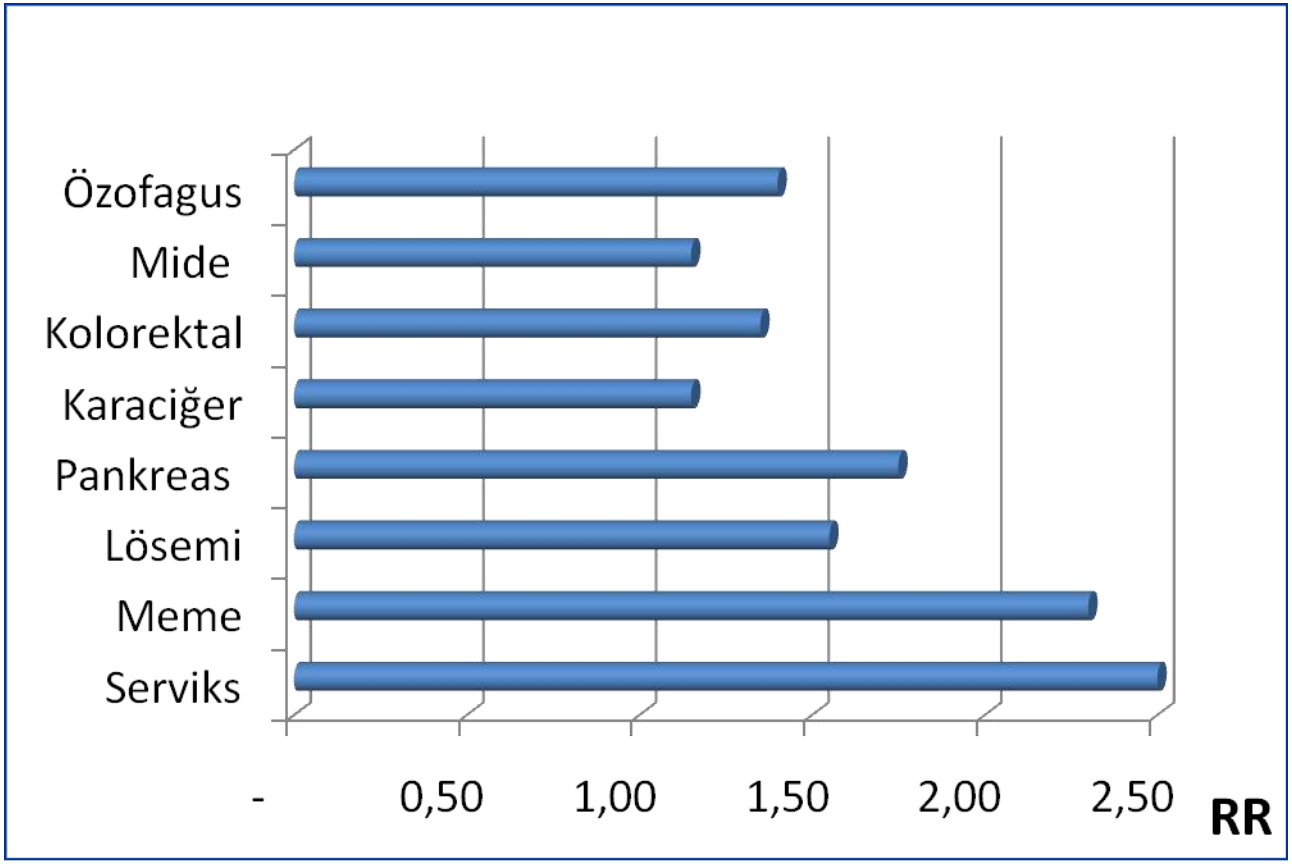
Son 10 Yılda Diayabetik Hastaların Dahil Edildiği Randomize Klinik Çalışmalardan Öğrendiklerimiz

ONKOLOJİK SONLANIM

Prof.Dr.Abdurrahman Çömlekçi
Dokuz Eylül Üniversitesi Tıp Fakültesi
Endokrinoloji Bilim Dalı
İZMİR

Diyabetlilerde kanser riski !



*kadınlarda serviks ve meme; erkeklerde diğerleri

WHO. The World Health Report, 2011.

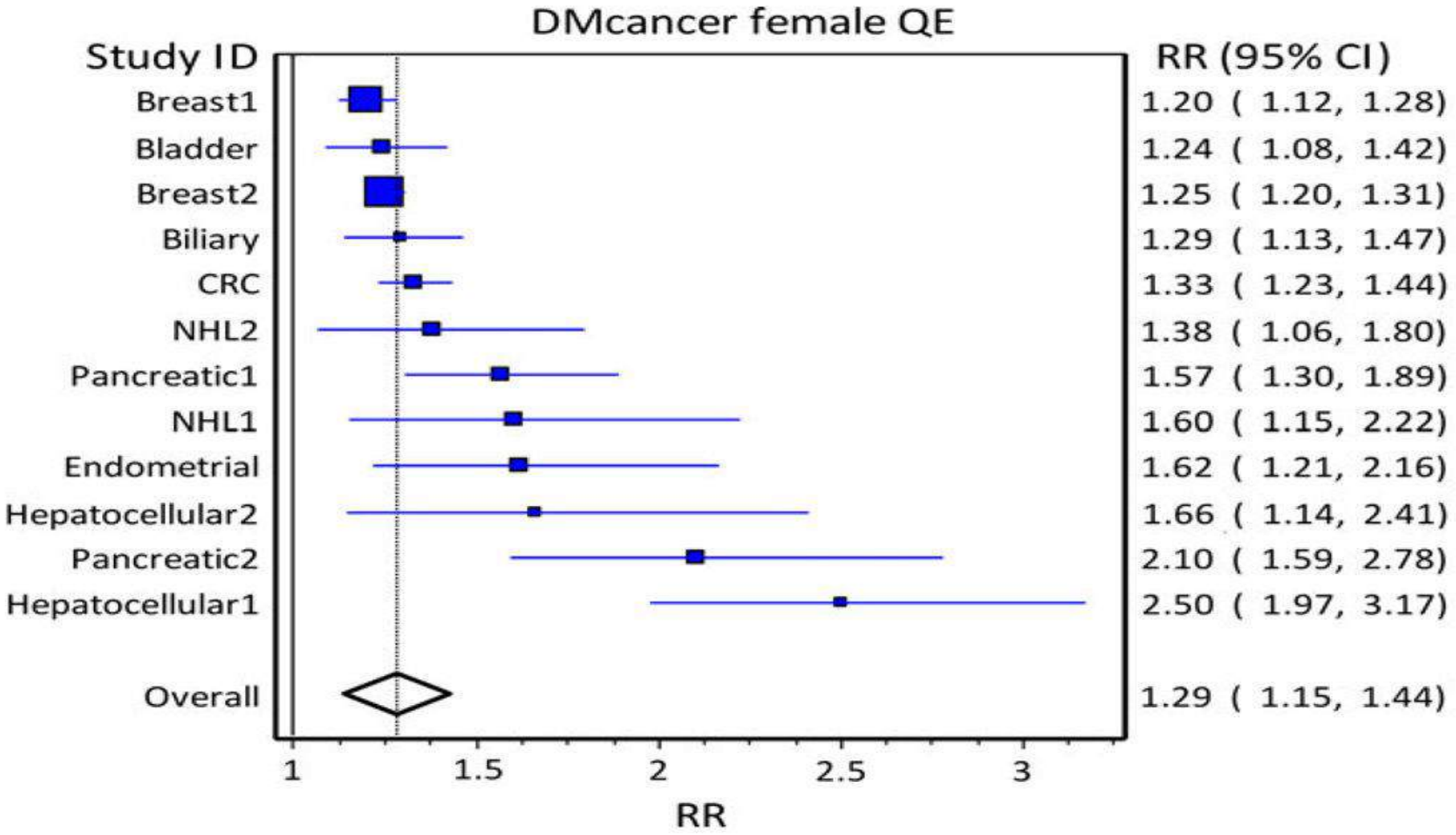
Diyabet ve kanser ilişkisi

Table 1 Meta-analyses on the relative risk (RR) of cancer in different organs of diabetic patients

Cancer		RR (95% CI)
Liver (El-Serag *et al.* 2006)	13 case–control studies	2.50 (1.8–3.5)
	7 cohort studies	2.51 (1.9–3.2)
Pancreas (Huxley *et al.* 2005)	17 case–control studies	1.94 (1.53–2.46)
	19 cohort studies	1.73 (1.59–1.88)
Kidney[a] (Lindblad *et al.* 1999, Washio *et al.* 2007)	1 cohort study	1.50 (1.30–1.70)
	1 cohort study	2.22 (1.04–4.70)
Endometrium (Friberg *et al.* 2007)	13 case–control studies	2.22 (1.80–2.74)
	3 cohort studies	1.62 (1.21–2.16)
Colon–rectum (Larsson *et al.* 2005)	6 case–control studies	1.36 (1.23–1.50)
	9 cohort studies	1.29 (1.16–1.43)
Bladder (Larsson *et al.* 2006)	7 case–control studies	1.37 (1.04–1.80)
	3 cohort studies	1.43 (1.18–1.74)
Non-Hodgkin's lymphoma (Mitri *et al.* 2008)	5 cohort studies	1.41 (1.07–1.88)
	11 case–control studies	1.12 (0.95–1.31)
Breast (Larsson *et al.* 2007)	5 case–control studies	1.18 (1.05–1.32)
	15 cohort studies	1.20 (1.11–1.30)
Prostate (Kasper & Giovannucci 2006)	9 case–control studies	0.89 (0.72–1.11)
	10 cohort studies	0.81 (0.71–0.92)

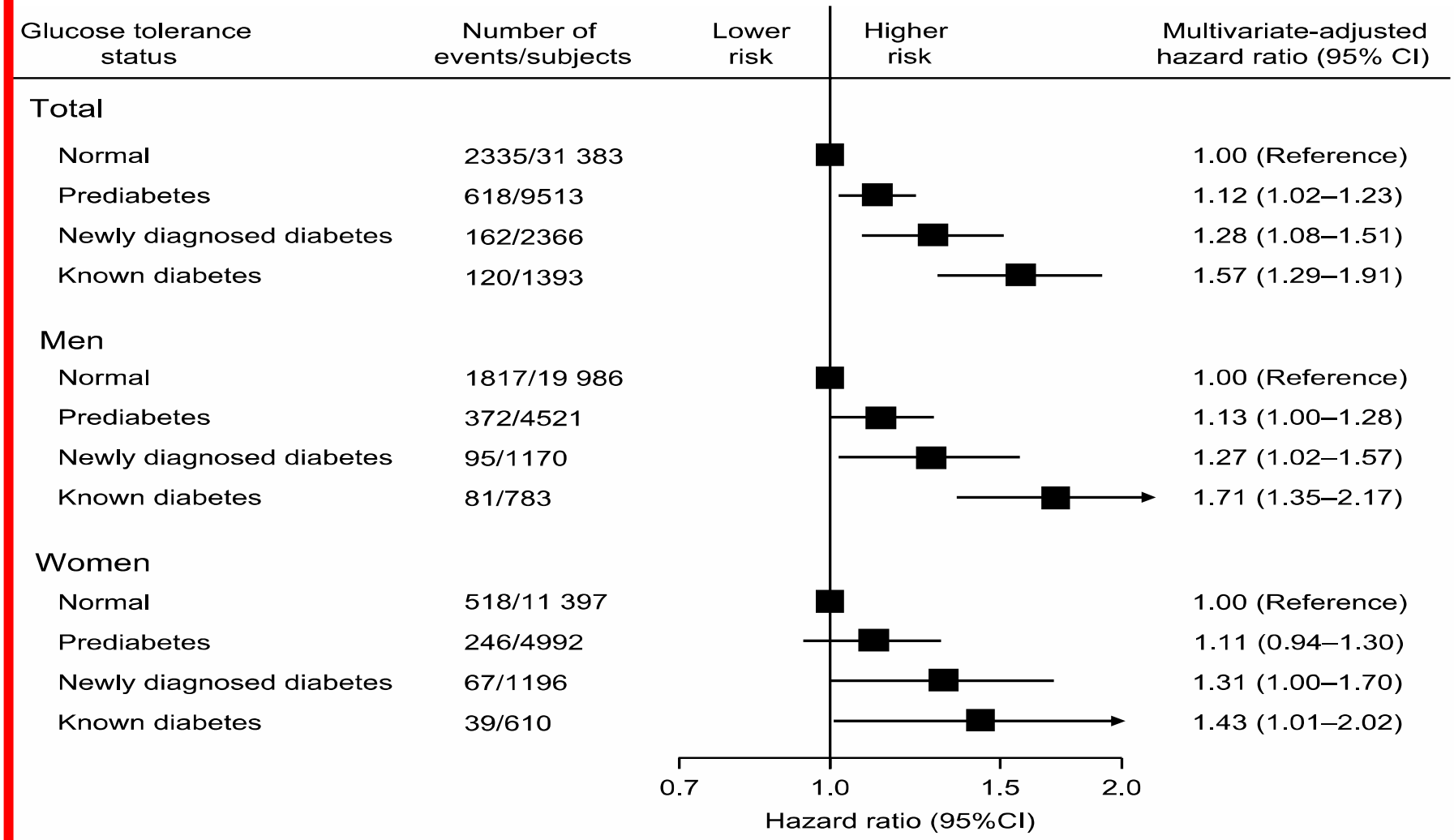
Vigneri P et al end related cancer 2009

DİYABET & KANSER & CİNSİYET



Onitilo et al 2012

Glukoz tolerans ve kanser riski



Shikata K cancer science 2012

Diyabet & Kanser & Mortalite

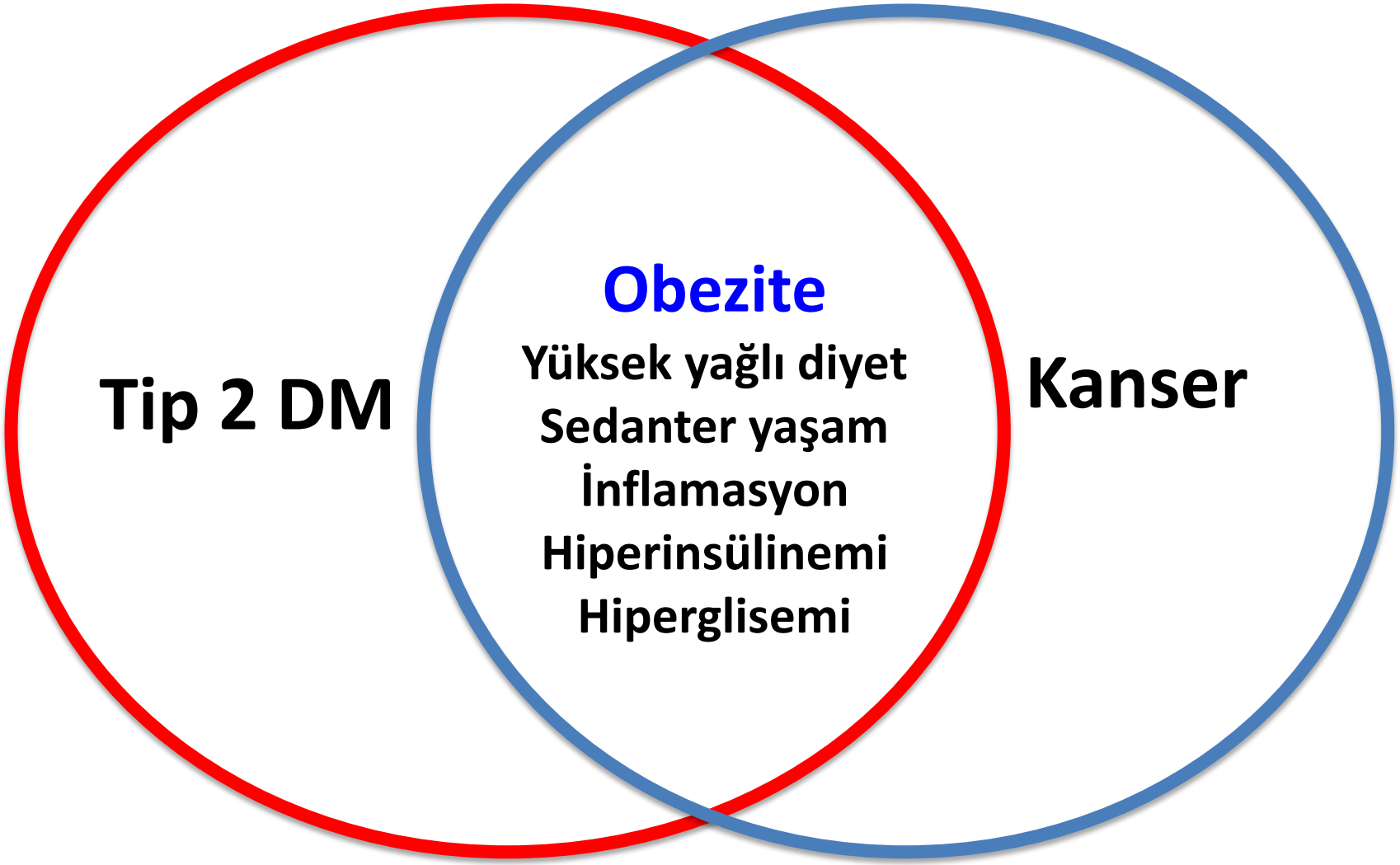
Cancer type	All-cause mortality		
	Ref. type	No. of studies (diabetes/no diabetes)[a]	Risk estimates (95% CI)
Increased incidence and mortality			
Colorectal	MA [24]	6 (8,028/46,712)	1.32 (1.24, 1.41)
Breast	MA [25]	4 (1,107/12,912)	1.49 (1.35, 1.65)
Endometrial	MA [22]	4 (429/2,471)	1.76 (1.34, 2.31)
Kidney	ECR [26]	1 (174/1,223)	33 vs 48% at 5 years
NHL	ECR [26]	1 (123/1,607)	32 vs 51% at 5 years
Increased incidence, no effect on mortality			
Pancreas	MA [22]	4 (477/1,204)	1.09 (0.70, 1.69)
Hepatocellular	MA [22]	3 (848/2,876)	1.30 (0.99, 1.70)
Decreased incidence/increased mortality			
Prostate	MA [23]	4 (555/5,709)	1.57 (1.12, 2.20)
No effect on incidence and mortality			
Lung	MA [22]	4 (989/10,120)	1.15 (0.99, 1.34)
Gastric	MA [22]	3 (687/5,513)	1.36 (0.92, 2.01)

A:G:Reneha et al Diabetologia 2012
Coughlin SS Am J Epidemiol 2004

ARTMIŞ MORTALİTE SEBEPLERİ

- Taramaların daha az yapılması
- Tanıda daha ileri evre hastalık
- Hiperinsülinemi ve ve hiperglisemi ortamında artmış tümör hücre proliferasyonu
- Daha az agresif tedaviler
- Kanser varlığında diyabetle ilgili komorbiditeler
- Kemoterapiye yanıtta yetersizlik
- Diyabet ilaçlarının kanser tedavisi üzerine etkisi
- Farklı tümör biyolojisi

Von De Poll-Franse Int J Cancer 2007Fleming et al Medical Care, 2005)

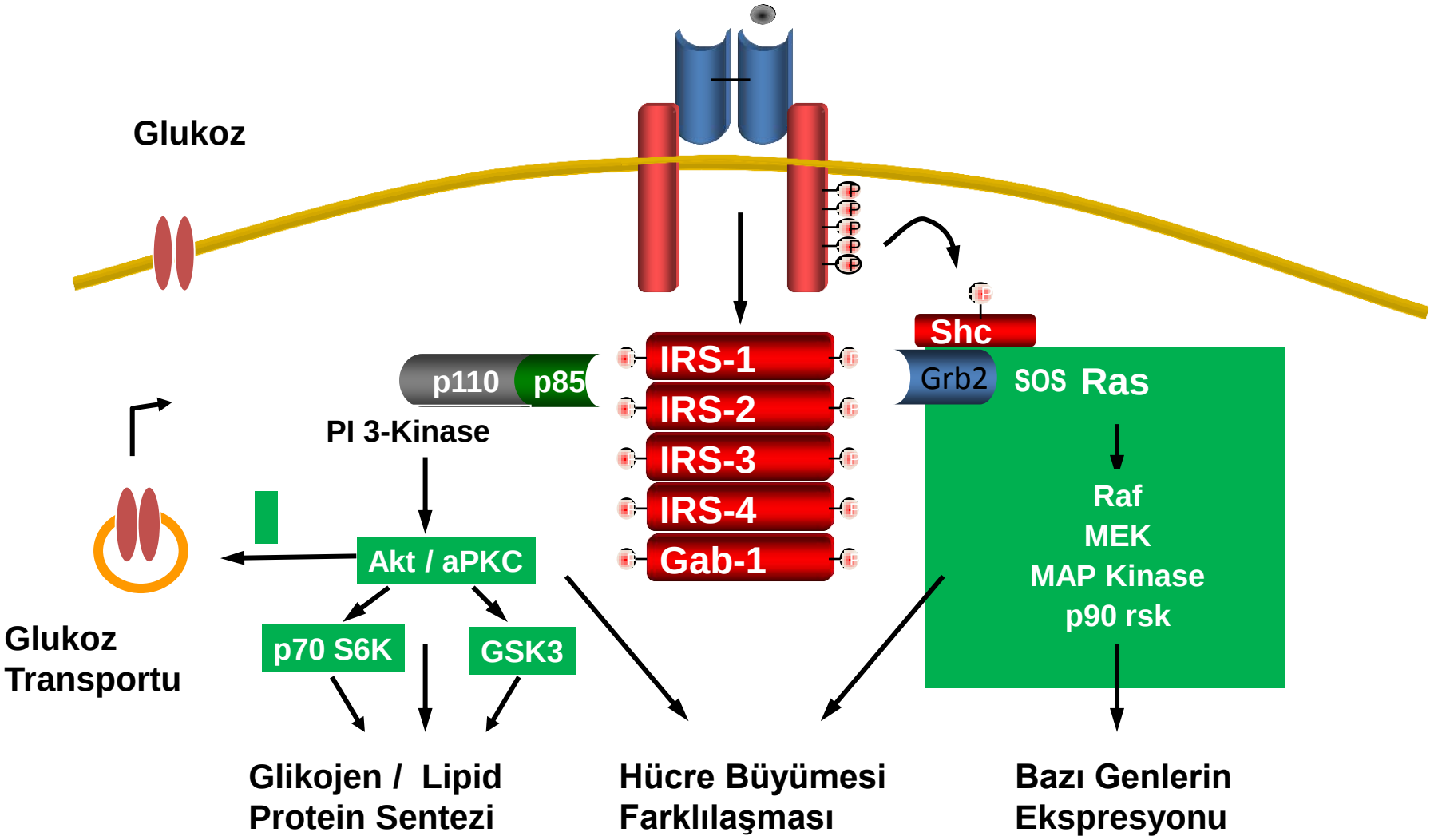

Tip 2 DM
Obezite
Yüksek yağlı diyet
Sedanter yaşam
İnflamasyon
Hiperinsülinemi
Hiperglisemi
Kanser

Etyopatogenezis...

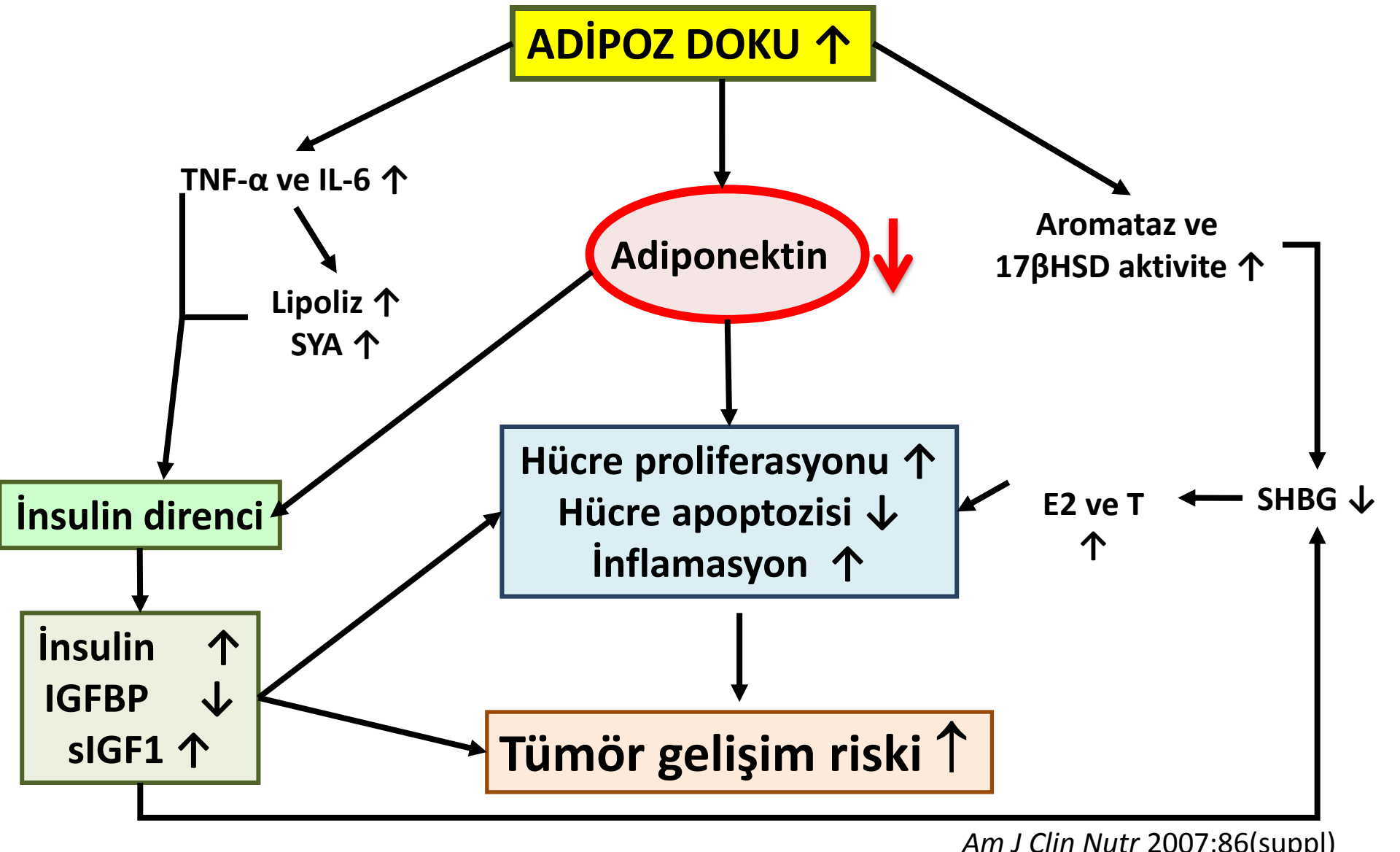
- ***Obezite***
- Hiperinsülinemi: İGF-1
- Seks steroidleri: Estrogen ve androgen
- SYA
- Adipokinler: Leptin ve adiponektin
- Kronik inflamasyon ve oksidatif stres: CRP, TNF-α,MCP-1, İL-1 , 6, 10,8
- NF-κB sistem
- ***Hiperglisemi***
- AGE-ROS-Mitokondrial disfonksiyon
- Enfeksiyonlar
- ***Kullanılan ilaçlar***

Vigneri et al. Endocrine-Related Cancer 2009

İnsulin Sinyal Ağı

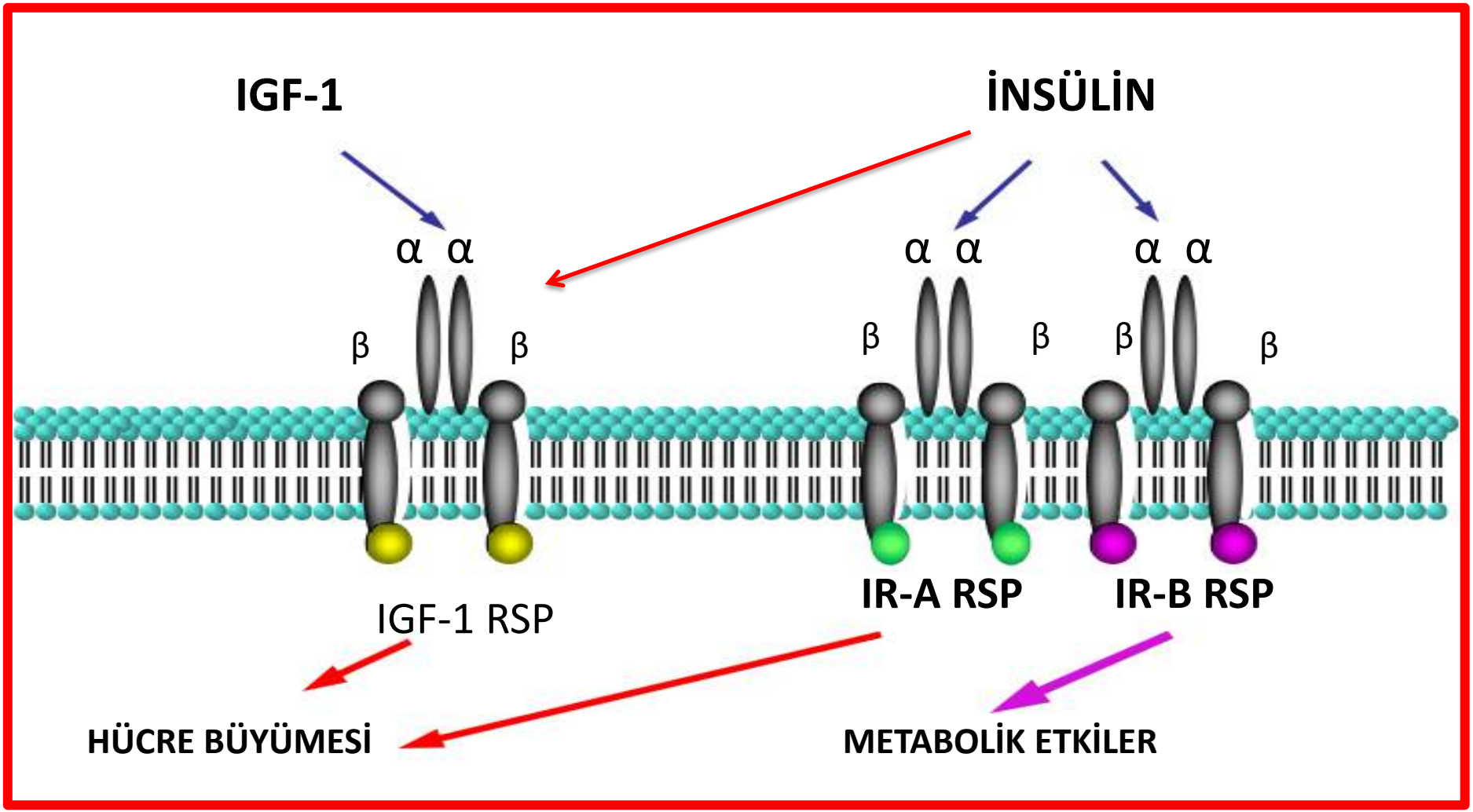


Obezitede Tümör Gelişim Riskinin Artış Mekanizmaları



Am J Clin Nutr 2007;86(suppl)

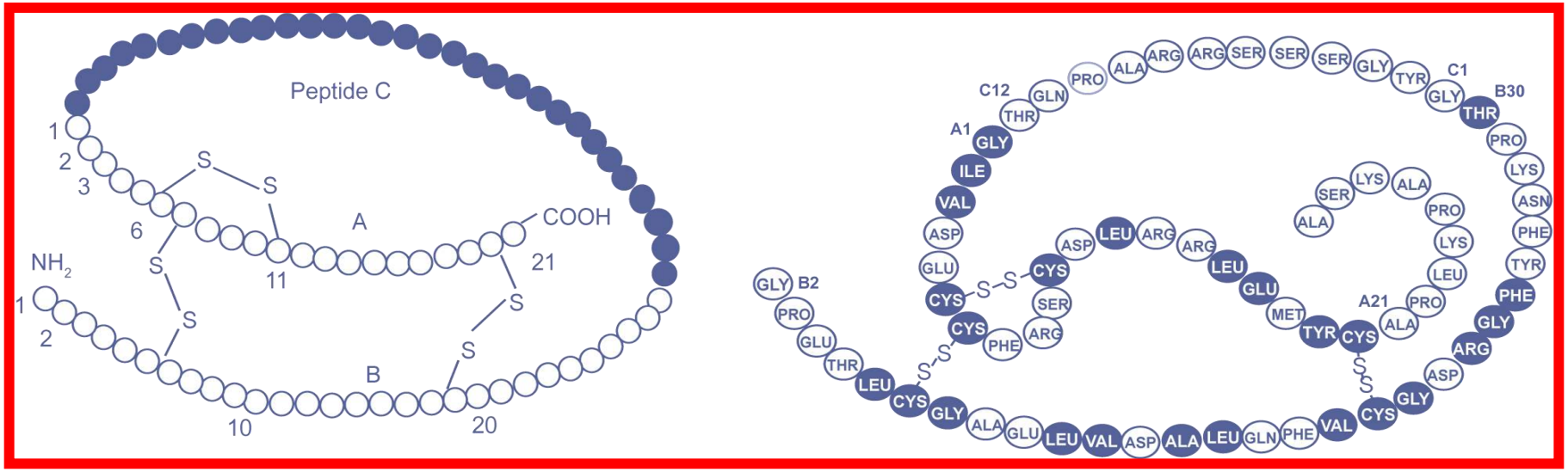
İNSÜLİN RESEPTÖR TİPLERİ



İnsülin ve IGF-1 aminoasit dizilimleri benzer

İnsan insülin

İnsan İGF-1



Metabolik aktivite ++

In vitro: yüksek konsantrasyonda mitojenik aktivite

Mitojenik aktivite ++[1,2]

In vitro: metabolik aktivite

[1]*Le Roith. N Engl J Med 1997;336:633–40.*

[2]*Holt, et al. Diabet Med 2003;20:3–15.*

İnsülin etkisi-Tümör gelişimi

- Mitojenik ve antiapopitotik
- Ras ‘ın fernastilasyonu ve Diğer büyüme faktörlerini etkilemesi (İGF-1)

- ERK ve PIP-3 yolak aktivasyonu
- β-katenin uyarısı,GSK-3β baskılanması ve Ras aktivasyonu
- Serbest serum İGF-1 düzeylerinde artış

Renehan et al. Archives of Physiology and Biochemistry, 2008

İGF-1 etkisi-Tümör gelişimi

- Mitojenik ve antiapopitotik
- Proanjiojenik, VEGF, HİF-1 ile artar
- Tümörde lenfangiogenez artar
- Hücre migrasyonu artar
- Östrojen gibi diğer potent büyüme faktörlerini aktive eder
- β-katenin lokalizasyonu, stabilizasyonu ve transkripsiyonel aktivitesini düzenler

Renehan et al. Archives of Physiology and Biochemistry, 2008

İlk Prospektif Çalışma (1959)

MEDICAL INTELLIGENCE

DIABETES AND CANCER*

ELLIOTT P. JOSLIN, M.D.,†
HERBERT L. LOMBARD, M.D.,‡
RUTH E. BURROWS, M.D.,§ AND
MIRIAM D. MANNING, M.D.¶

BOSTON

- **1026 diabetes patients followed x 15 years**
- **Number of cancer cases in diabetes patients did not differ significantly from expected rate**

İNSÜLİNLER/MİTOJENİTE

		Metabolik potens	IGF-I reseptör afinitesi	IGF-IR/IR affinitesi	Mitojenik potens (Saos/B10 hücreleri)
Human insülin	100	100	100	1	100
B10 Asp	205 ± 20	207 ± 14	587 ± 50	2.9	975 ± 173
İnsülin lispro	84 ± 6	82 ± 3	156 ± 16	0.9	66 ± 10
İnsülin aspart	92 ± 6	101 ± 2	81 ± 9	1.9	58 ± 22
İnsülin glargine	86 ± 3	60 ± 3	641 ± 51	7.5	783 ± 13
İnsülin detemir	~18 - 46	~ 27	16 ± 1	0.9	~ 11

Kurtzhals et al. Diabetes 2000;49:999.

Diabetologia
DOI 10.1007/s00125-009-1418-4

ARTICLE

Risk of malignancies in patients with diabetes treated with human insulin or insulin analogues: a cohort study

L. G. Hemkens · U. Grouven · R. Bender · C. Günster · S. Gutschmidt · G. W. Selke · P. T. Sawicki

Abstract

Aims/hypothesis The aim of this cohort study was to investigate the risk of malignant neoplasms and mortality in patients with diabetes treated either with human insulin or with one of three insulin analogues.

Methods Data were provided by the largest German statutory health insurance fund (time-frame: January 1998 to June 2005 inclusive), on patients without known malignant disease who had received first-time therapy for diabetes mellitus exclusively with human insulin, aspart, lispro or glargine. The primary outcome was the diagnosis of a malignant neoplasm. Data were analysed by multiple Cox regression models adjusting for potential confounders.

Results A total of 127,031 patients were included, with a mean follow-up time of 1.63 (median 1.41, maximum 4.41) years. A positive association between cancer incidence and insulin dose was found for all insulin types. Because patients receiving combined therapy with insulin analogues and human insulin were excluded, the mean daily dose was much lower for glargine than for human insulin, and a slightly lower cancer incidence in the glargine group was found. After adjusting for dose, a dose-dependent increase in cancer risk was found for treatment with glargine compared with human insulin ($p<0.0001$): the adjusted HR was 1.09 (95% CI 1.00 to 1.19) for a daily dose of 10 IU, 1.19 (95% CI 1.10 to 1.30) for a daily dose of 30 IU, and 1.31 (95% CI 1.20 to 1.42) for a daily dose of 50 IU. No increased risk was found for aspart ($p=0.30$) or lispro ($p=0.96$) compared with human insulin.

Conclusions/interpretation Considering the overall relationship between insulin dose and cancer, and the lower dose with glargine, the cancer incidence with glargine was higher than expected compared with human insulin. Our results based on observational data support safety concerns surrounding the mitogenic properties of glargine in diabetic patients. Prospective long-term studies are needed to further evaluate the safety of insulin analogues, especially glargine.

Diabetologia
DOI 10.1007/s00125-009-1440-6

ARTICLE

The influence of glucose-lowering therapies on cancer risk in type 2 diabetes

C. J. Currie · C. D. Poole · E. A. M. Gale

Abstract

Aims/hypothesis The risk of developing a range of solid tumours is increased in type 2 diabetes, and may be influenced by glucose-lowering therapies. We examined the risk of development of solid tumours in relation to treatment with oral agents, human insulin and insulin analogues.

Methods This was a retrospective cohort study of people treated in UK general practices. Those included in the analysis developed diabetes >40 years of age, and started treatment with oral agents or insulin after 2000. A total of 62,809 patients were divided into four groups according to whether they received monotherapy with metformin or sulfonylurea, combined therapy (metformin plus sulfonylurea), or insulin. Insulin users were grouped according to treatment with insulin glargine, long-acting human insulin, biphasic analogue and human biphasic insulin. The outcome measures were progression to any solid tumour, or cancer of the breast, colon, pancreas or prostate. Confounding factors were accounted for using Cox proportional hazards models.

Results Metformin monotherapy carried the lowest risk of cancer. In comparison, the adjusted HR was 1.08 (95% CI 0.96–1.21) for metformin plus sulfonylurea, 1.36 (95% CI 1.19–1.54) for sulfonylurea monotherapy, and 1.42 (95% CI 1.27–1.60) for insulin-based regimens. Adding metformin to insulin reduced progression to cancer (HR 0.54, 95% CI 0.43–0.66). The risk for those on basal human insulin alone vs insulin glargine alone was 1.24 (95% CI 0.90–1.70). Compared with metformin, insulin therapy increased the risk of colorectal (HR 1.69, 95% CI 1.23–2.33) or pancreatic cancer (HR 4.63, 95% CI 2.64–8.10), but did not influence the risk of breast or prostate cancer. Sulfonylureas were associated with a similar pattern of risk as insulin.

Conclusions/interpretation Those on insulin or insulin secretagogues were more likely to develop solid cancers than those on metformin, and combination with metformin abolished most of this excess risk. Metformin use was associated with lower risk of cancer of the colon or pancreas, but did not affect the risk of breast or prostate cancer. Use of insulin analogues was not associated with increased cancer risk as compared with human insulin.

Keywords Cancer · Insulin · Insulin analogues · Metformin · Sulfonylureas · Survival · Type 2 diabetes

Diabetologia
DOI 10.1007/s00125-009-1444-2

ARTICLE

Insulin glargine use and short-term incidence of malignancies—a population-based follow-up study in Sweden

J. M. Jonasson · R. Ljung · M. Talbäck · B. Haglun
S. Gudbjörnsdòttir · G. Steineck

Received: 26 May 2009 / Accepted: 18 June 2009

Abstract
Aims/hypothesis In the light of a report suggesting that insulin glargine may increase cancer occurrence, the EASD asked us to perform this study.
Methods We followed 114,841 individuals who had a prescription dispensed for insulin between 1 July and 31 December 2005. From 1 January 2006 to 31 December 2007, we noted the occurrence of malignancies. Seven different nationwide registers were used to obtain information on insulin exposure, outcome and possible confounders; these were linked using the unique personal identity number assigned to every Swedish resident.
Results After adjustment for age and, when appropriate, sex, users of insulin glargine alone (no other types of insulin), compared with users of types of insulin other than insulin glargine, had an RR of 1.99 (95% CI 1.31–3.03) for breast cancer, 0.93 (95% CI 0.61–1.40) for gastrointestinal cancer, 1.27 (95% CI 0.89–1.82) for prostate cancer and 1.07 (95% CI 0.91–1.27) for any type of malignancy. Adjustment for age, smoking, BMI, age at onset of diabetes, age at birth of first child, cardiovascular disease and oestrogen use gave an RR for breast cancer of 1.97 (95% CI 1.29–3.00). The 95% CIs crossed 1.0 for the RR calculated in all analyses of users of insulin glargine in combination with other types of insulin.
Conclusions/interpretation In Sweden, during 2006 and 2007, women using insulin glargine alone (no other types of insulin) had an increased incidence rate of breast cancer as compared with women using types of insulin other than insulin glargine. This result may be due to a random fluctuation; the possibilities for examining validity are limited, and no statistically significant results were obtained for any other individual cancer site or for the outcome 'all malignancies'. No definitive conclusions regarding a possible causal relationship between insulin glargine use and the occurrence of malignancies can be drawn from the results of this study.

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Diabetologia (2009) 52:1755–1765
DOI 10.1007/s00125-009-1453-1

ARTICLE

Use of insulin glargine and cancer incidence in Scotland: a study from the Scottish Diabetes Research Network Epidemiology Group

H. M. Colhoun · SDRN Epidemiology Group

Received: 5 June 2009 / Ac

Abstract

Aims/hypothesis The aim of the present study was to examine whether patients with diabetes in Scotland using insulin glargine have a greater cancer risk than patients using other types of insulin.

Methods We used a nationwide diabetes clinical database that covers the majority of the Scottish population with diagnosed diabetes, and examined patients with diabetes who were exposed to any insulin therapy between 1 January 2002 and 31 December 2005. Among these we defined a fixed cohort based on exposure during a 4 month period in 2003 (n=36,254, in whom 715 cases of cancer occurred) and a cohort of new insulin users across the period (n=12,852 in whom 381 cancers occurred). Records from these cohorts were linked to cancer registry data up to the end of 2005. We used Cox proportional hazards models for survival analyses.

Results Those receiving any insulin glargine (n=3,959) had the same incidence rate for all cancers as those not receiving insulin glargine (HR 1.02, 95% CI 0.77–1.36, p=0.9 in the fixed cohort) The subset of patients using insulin glargine alone (n=447) had a significantly higher incidence of all cancers than those using other insulins only (n=32,295) (HR 1.55, 95% CI 1.01–2.37, p=0.045), and those using insulin glargine with other insulins (n=3,512) had a slightly lower incidence (HR 0.81, 95% CI 0.55–1.18, p=0.26). There were important differences in baseline characteristics between these three groups, although the risk ratios were broadly unaltered on adjustment for these. Overall, there was no increase in breast cancer rates associated with insulin glargine use (HR 1.49, 95% CI 0.79–2.83, though insulin glargine only users had a higher rate than those using non-glargine insulin only (HR 3.39, 95% CI 1.46–7.85, p=0.004). Among type 2 diabetic incident insulin users, no significant difference between the three groups was observed with respect to all cancer or breast cancer. All the above HRs are adjusted for age, calendar time prior cancer and type of diabetes, as appropriate, and are stratified according to sex.

Conclusions/interpretation Overall, insulin glargine use was not associated with an increased risk of all cancers or site-specific cancers in Scotland over a 4 year time frame. Given the overall data, we consider the excess of cases of all cancers and breast cancer in the subgroup of insulin glargine only users to more likely reflect allocation bias rather than an effect of insulin glargine itself.

The SDRN Epidemiology Group members involved in this study were (in alphabetical order): S. Brearley, University of Dundee; J. Chalmers, NHS Fife; H. M. Colhoun, University of Dundee & NHS Fife; S. Cunningham, University of Dundee; A. Emslie-Smith, GP & University of Dundee; C. Fischbacher, ISD Scotland; R. Lindsay, University of Glasgow; S. Livingstone, University of Dundee; R. McAlpine, University of Dundee; J. McKnight, University of

Effect of Long-Acting Insulin Analogs on the Risk of Cancer: A Systematic Review of Observational Studies

Jennifer W. Wu,[1,2] Kristian B. Filion,[1,2,3] Laurent Azoulay,[1,2,4] Margaret K. Doll,[1] and Samy Suissa[1,2,3]

Diabetes Care 2016;39:486–494 | DOI: 10.2337/dc15-1816

OBJECTIVE

Observational studies examining the association between long-acting insulin analogs and cancer incidence have produced inconsistent results. We conducted a systematic review of these studies, focusing on their methodological strengths and weaknesses.

RESEARCH DESIGN AND METHODS

We systematically searched MEDLINE and EMBASE from 2000 to 2014 to identify all observational studies evaluating the relationship between the long-acting insulin analogs and the risk of any and site-specific cancers (breast, colorectal, prostate). We included cohort and case-control studies published in English on insulin glargine and detemir and any cancer incidence among patients with type 1 or 2 diabetes. The methodological assessment involved the inclusion of prevalent users, inclusion of lag periods, time-related biases, and duration of follow-up between insulin initiation and cancer incidence.

RESULTS

A total of 16 cohort and 3 case-control studies met our inclusion criteria. All studies evaluated insulin glargine, and four studies also examined insulin detemir. Follow-up ranged from 0.9 to 7.0 years. Thirteen of 15 studies reported no association between insulin glargine and detemir and any cancer. Four of 13 studies reported an increased risk of breast cancer with insulin glargine. In the quality assessment, 7 studies included prevalent users, 11 did not consider a lag period, 6 had time-related biases, and 16 had short (<5 years) follow-up.

CONCLUSIONS

The observational studies examining the risk of cancer associated with long-acting insulin analogs have important methodological shortcomings that limit the conclusions that can be drawn. Thus, uncertainty remains, particularly for breast cancer risk.

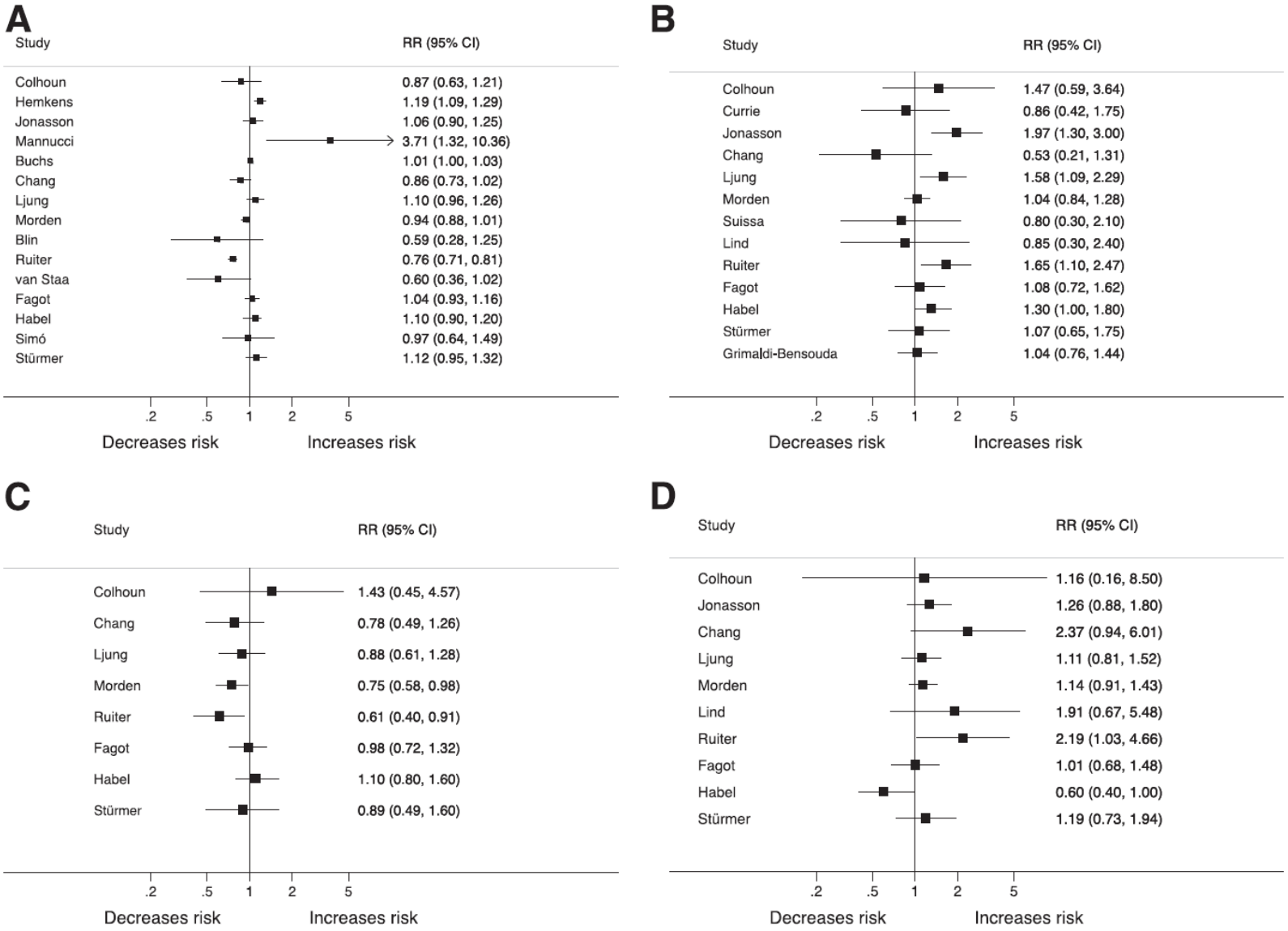

Figure 1—Forest plots of RRs (solid squares) and 95% CIs (solid horizontal lines) from studies on insulin glargine and any (*A*), breast (*B*), colorectal (*C*), and prostate (*D*) cancers. For exposure and comparator definitions in each study, please refer to Table 1.

Table 2—Pharmacoepidemiology biases in studies examining the association between long-acting insulin analogs and cancer incidence

Study	Short follow-up*	Prevalent insulin users†	Lack of lag period	Residual confounding‡	Time-related biases: Immortal time	Time-related biases: Time-lag	Time-related biases: Time-window	Main limitation§
Colhoun (5)	•			•				Short follow-up
Currie (6)	•		•	•				Short follow-up
Hemkens (7)	•		•	•		•		Time-lag bias
Jonasson (8)	•	•		•				Inclusion of prevalent users
Mannucci (22)				•			•	Time-window bias
Buchs (15)	•	•	•	•				Inclusion of prevalent users
Chang (16)	•		•	•				Selection bias and lack of lag period
Ljung (21)	•	•	•	•				Inclusion of prevalent users
Morden (23)	•	•	•	•		•		Time-lag bias
Suissa (27)	•			•				Short follow-up
Blin (14)	•		•	•	•	•		Immortal time bias
Lind (20)		•	•	•				Inclusion of prevalent users
Ruiter (24)	•			•				Short follow-up
van Staa (28)	•		•	•		•		Time-lag bias
Fagot (17)	•			•				Short follow-up
Habel (19)	•		•	•				Lack of lag period
Simó (25)	•	•		•				Inappropriate comparator
Stürmer (26)	•			•				Short follow-up
Grimaldi-Bensouda (18)		•	•	•			•	Selection bias

•Indicates presence of the methodological issue or bias in the study. *Short follow-up is defined as <5 years of follow-up. †Prevalent insulin users refers to the study not distinguishing between prevalent and new insulin users. ‡Residual confounding as a result of unmeasured confounders (HbA_{1c} and diabetes duration) or lack of adjustments for time-dependent confounders. §Main limitation refers to bias or methodological issue that changed the RR.

Risk of Breast Cancer by Individual Insulin Use: An International Multicenter Study

Lamiae Grimaldi-Bensouda,[1] David Cameron,[2] Michel Marty,[3] Anthony H. Barnett,[4] Frédérique Penault-Llorca,[5] Michael Pollak,[6] Bernard Charbonnel,[7] Matthew Riddle,[8] Laurent Mignot,[9] Jean-François Boivin,[10] Artak Khachatryan,[11] Michel Rossignol,[12] Jacques Bénichou,[13] Annick Alpérovitch,[14] and Lucien Abenhaim,[11,15] for the ISICA Group

Table 3—Individual insulin use and risk of breast cancer

	Case subjects	Matched control subjects	Crude matched OR (95% CI)*	Adjusted matched OR (95% CI)*¥
N	775	3,050		
Use of a specific insulin in the 8-year prior to index date vs. no use of that insulin**				
Glargine	78 (10.1)	287 (9.4)	0.99 (0.74–1.34)	1.04 (0.76–1.44)
Lispro	46 (5.9)	133 (4.4)	1.24 (0.84–1.84)	1.23 (0.79–1.92)
Aspart	54 (7.0)	241 (7.9)	0.86 (0.61–1.21)	0.95 (0.64–1.40)
Human insulin	59 (7.6)	260 (8.5)	0.81 (0.57–1.13)	0.81 (0.55–1.20)
Any insulin use prior to the 8-year observation period vs. no use of any insulin	74 (9.5)	270 (8.9)	0.97 (0.69–1.35)	0.95 (0.62–1.45)
Glargine dose vs. all other users of insulin§				
N	144	410		
No glargine	70 (48.6)	207 (50.5)	1.00	1.00
Any dose	74 (51.4)	203 (49.5)	1.08 (0.71–1.64)	0.96 (0.61–1.53)
Low dose	31 (21.5)	89 (21.7)	1.17 (0.68–2.00)	1.10 (0.61–1.97)
High dose	33 (22.9)	87 (21.2)	1.05 (0.63–1.75)	1.02 (0.59–1.75)
Undefined dose	10 (6.9)	27 (6.6)	0.94 (0.42–2.14)	0.85 (0.35–2.07)

Data are *n* (%) unless otherwise indicated. *Control subjects matched to case subjects by type of diabetes (1 or 2), age, date of recruitment, region/country, and referral to diabetologist (yes/no). ¥Adjusted matched ORs obtained from conditional logistic regressions controlled for age, breast cancer risk score, BMI (≤24, 25–29, and ≥30 kg/m^2), comorbidities (<3 or ≥3), duration of diabetes (<10 years or ≥10 years), no. of visits to physician/year, and oral antidiabetes drug use. In addition, adjusted ORs for individual insulin molecules were further adjusted for other insulin use (animal, glulisine, detemir, or unclassified, as a separate category, yes/no) and past insulin use (any insulin use ≥8 years before index date). **Index date, date of first pathological confirmation of breast cancer. §High and low dose dichotomized at the median dose (27 IU) for all glargine users: low dose, no dose above the median reported; high dose, use above the median reported at least once.

Risk of Breast Cancer by Individual Insulin Use: An International Multicenter Study

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OBJECTIVE

Several studies have been published in 2009 suggesting a possible association between insulin glargine and increased risk of malignancies, including breast cancer. The objective of this study was to assess the relation between the individual insulins (glargine, aspart, lispro, and human insulin) and development of breast cancer.

RESEARCH DESIGN AND METHODS

Seven hundred seventy-five incident cases of primary invasive or in situ carcinoma breast cancer occurring in women with diabetes from 92 centers in the U.K., Canada, and France were matched to a mean of 3.9 diabetic community control subjects (*n* = 3,050; recruited from 580 general practices) by country, age, recruitment date, and diabetes type and management. The main risk model was a multivariate conditional logistic regression model with case/control status as the dependent variable and individual insulin use, 8 years preceding the index date, as the independent variable, controlling for past use of any insulin, oral antidiabetes drugs, reproductive factors, lifestyle, education, hormone replacement therapy and history of contraceptive use, BMI, comorbidities, diabetes duration, and annual number of physician visits. Glargine was also compared with every other insulin by computing all ratios using the variance-covariance matrix of logistic model parameters.

RESULTS

Adjusted odds ratios of breast cancer for each type of insulin versus no use of that insulin were 1.04 (95% CI 0.76–1.44) for glargine, 1.23 (0.79–1.92) for lispro, 0.95 (0.64–1.40) for aspart, and 0.81 (0.55–1.20) for human insulin. Two-by-two comparisons found no difference between glargine and the different types of insulins. Insulin dosage or duration of use and tumor stage did not change the results.

CONCLUSIONS

This international study found no difference in the risk of developing breast cancer in patients with diabetes among the different types of insulin with short- to mid-term duration of use. Longer-term studies would be of interest.

Diabetes Care 2014;37:134–143 | DOI: 10.2337/dc13-0695

Table 3—Individual insulin use and risk of breast cancer

	Case subjects	Matched control subjects	Crude matched OR (95% CI)*	Adjusted matched OR (95% CI)*¥
N	775	3,050		
Use of a specific insulin in the 8-year prior to index date vs. no use of that insulin**				
Glargine	78 (10.1)	287 (9.4)	0.99 (0.74–1.34)	1.04 (0.76–1.44)
Lispro	46 (5.9)	133 (4.4)	1.24 (0.84–1.84)	1.23 (0.79–1.92)
Aspart	54 (7.0)	241 (7.9)	0.86 (0.61–1.21)	0.95 (0.64–1.40)
Human insulin	59 (7.6)	260 (8.5)	0.81 (0.57–1.13)	0.81 (0.55–1.20)
Any insulin use prior to the 8-year observation period vs. no use of any insulin	74 (9.5)	270 (8.9)	0.97 (0.69–1.35)	0.95 (0.62–1.45)
Glargine dose vs. all other users of insulin§				
N	144	410		
No glargine	70 (48.6)	207 (50.5)	1.00	1.00
Any dose	74 (51.4)	203 (49.5)	1.08 (0.71–1.64)	0.96 (0.61–1.53)
Low dose	31 (21.5)	89 (21.7)	1.17 (0.68–2.00)	1.10 (0.61–1.97)
High dose	33 (22.9)	87 (21.2)	1.05 (0.63–1.75)	1.02 (0.59–1.75)
Undefined dose	10 (6.9)	27 (6.6)	0.94 (0.42–2.14)	0.85 (0.35–2.07)

Data are *n* (%) unless otherwise indicated. *Control subjects matched to case subjects by type of diabetes (1 or 2), age, date of recruitment, region/country, and referral to diabetologist (yes/no). ¥Adjusted matched ORs obtained from conditional logistic regressions controlled for age, breast cancer risk score, BMI (≤24, 25–29, and ≥30 kg/m^2), comorbidities (<3 or ≥3), duration of diabetes (<10 years or ≥10 years), no. of visits to physician/year, and oral antidiabetes drug use. In addition, adjusted ORs for individual insulin molecules were further adjusted for other insulin use (animal, glulisine, detemir, or unclassified, as a separate category, yes/no) and past insulin use (any insulin use ≥8 years before index date). **Index date, date of first pathological confirmation of breast cancer. §High and low dose dichotomized at the median dose (27 IU) for all glargine users: low dose, no dose above the median reported; high dose, use above the median reported at least once.

ORIGINAL ARTICLE

Basal Insulin and Cardiovascular and Other Outcomes in Dysglycemia

The ORIGIN Trial Investigators*

12537
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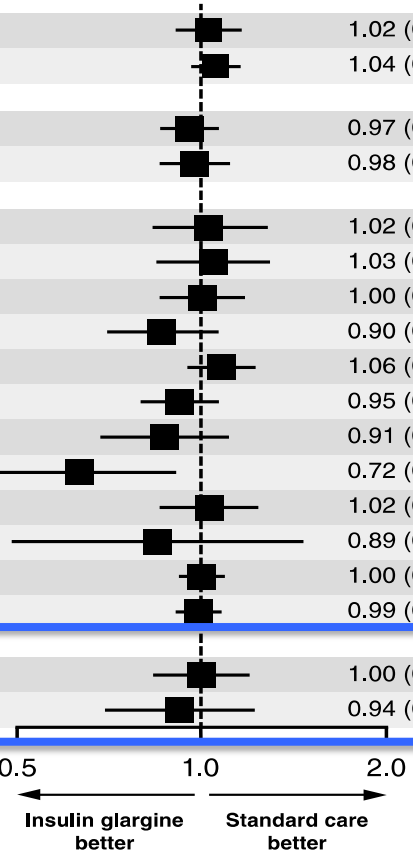
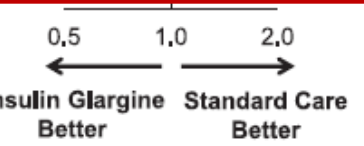
Outcome	Insulin Glargine (N=6264)		Standard Care (N=6273)		Hazard Ratio (95% CI)	p Value
	no. (%)	no./100 patient-yr	no. (%)	no./100 patient-yr		
First coprimary outcome	1041 (16.6)	2.94	1013 (16.1)	2.85	1.02 (0.94–1.11)	0.63
Second coprimary outcome	1792 (28.6)	5.52	1727 (27.5)	5.28	1.04 (0.97–1.11)	0.27
Microvascular outcomes	1323 (21.1)	3.87	1363 (21.7)	3.99	0.97 (0.90–1.05)	0.43
Total mortality	951 (15.2)	2.57	965 (15.4)	2.60	0.98 (0.90–1.08)	0.70
Total myocardial infarctions	336 (5.4)	0.93	326 (5.2)	0.90	1.02 (0.88–1.19)	0.75
Total strokes	331 (5.3)	0.91	319 (5.1)	0.88	1.03 (0.89–1.21)	0.69
Death from cardiovascular causes	580 (9.3)	1.57	576 (9.2)	1.55	1.00 (0.89–1.13)	0.98
Hospitalization from congestive heart failure	310 (4.9)	0.85	343 (5.5)	0.95	0.90 (0.77–1.05)	0.16
Revascularization	908 (14.5)	2.69	860 (13.7)	2.52	1.06 (0.96–1.16)	0.24
Angina	709 (11.3)	2.07	743 (11.8)	2.17	0.95 (0.85–1.05)	0.29
Unstable	238 (3.8)	0.66	261 (4.2)	0.72	0.91 (0.76–1.08)	0.28
New	100 (1.6)	0.27	138 (2.2)	0.38	0.72 (0.56–0.93)	0.01
Worsening	455 (7.3)	1.29	446 (7.1)	1.26	1.02 (0.89–1.16)	0.80
Limb or digit amputation	47 (0.8)	0.13	53 (0.8)	0.14	0.89 (0.60–1.31)	0.55
Cardiovascular hospitalization	2081 (33.2)	6.98	2071 (33.0)	6.91	1.00 (0.94–1.07)	0.90
Noncardiovascular hospitalization	2339 (37.3)	7.90	2349 (37.4)	7.93	0.99 (0.94–1.05)	0.85
Any cancer	476 (7.6)	1.32	477 (7.6)	1.32	1.00 (0.88–1.13)	0.97
Death from cancer	89 (3.0)	0.51	201 (3.2)	0.54	0.94 (0.77–1.15)	0.52



Standart Bakıma Karşı İnsülin Glarjin: Kardiyovasküler, Mikrovasküler ve Kanser Sonlanımları

Yüksek KV riske sahip IFG+IGT+T2DM'lilerde insülin glarjin ile sağlanan normoglisemi; 2.7 yıl daha uzatılarak izlendiğinde **(~ 9 yıllık takibin sonunda)** KV, mikrovasküler ve kanser sonlanımlarında artışa neden olmadan metabolik duruma katkı sağladığı görülmüş (olumlu miras)

	Insulin Glargine		Standard Care		Hazard Ratio	P
	Events	/100 py	Events	/100 py	(95%CI)	
First coprimary outcome	1185	2.95	1165	2.89	1.01 (0.94-1.10)	0.72
Second coprimary outcome	1958	5.38	1910	5.19	1.03 (0.97-1.10)	0.38
Clinical microvascular outcomes	221	0.53	249	0.60	0.89 (0.74-1.07)	0.20
Total mortality	1136	2.65	1158	2.69	0.98 (0.90-1.06)	0.63
Total myocardial infarctions	368	0.90	359	0.88	1.02 (0.88-1.18)	0.76
Total strokes	356	0.87	339	0.82	1.05 (0.90-1.21)	0.57
Death from cardiovascular causes	694	1.62	695	1.62	1.00 (0.90-1.11)	0.94
Hospitalization for congestive heart failure	336	0.82	370	0.90	0.90 (0.78-1.05)	0.18
Revascularization	972	2.56	934	2.43	1.04 (0.95-1.14)	0.35
Angina	741	1.92	779	2.02	0.94 (0.85-1.04)	0.24
Limb or digit amputation	50	0.12	62	0.15	0.81 (0.55-1.17)	0.25
Cardiovascular hospitalization	2168	6.55	2167	6.49	1.00 (0.94-1.06)	0.96
Any cancer	524	1.28	529	1.29	0.99 (0.88-1.12)	0.91
Death from cancer	225	0.52	236	0.55	0.95 (0.79-1.14)	0.61



Punthakee Z. , ORIGIN Trial Investigators, Diabetes Care December 17, 2015, doi: 10.2337/dc15-1676

Cohort Study of Pioglitazone and Cancer Incidence in Patients With Diabetes

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LAUREL A. HABEL, PHD[1]

OBJECTIVE—To explore whether treatment with pioglitazone was associated with risk of incident cancer at the 10 most common sites (prostate, female breast, lung/bronchus, endometrial, colon, non-Hodgkin lymphoma [NHL], pancreas, kidney/renal pelvis, rectal, and melanoma).

RESEARCH DESIGN AND METHODS—A cohort study of 252,467 patients aged ≥40 years from the Kaiser Permanente Northern California Diabetes Registry was conducted. All prescriptions for diabetes medications were identified by pharmacy records. Cox proportional hazards models were used to examine the association between risk of incident cancer and ever use, duration, dose, and time since initiation of pioglitazone (modeled as time-dependent variables).

RESULTS—In models adjusted for age, sex, year of cohort entry, race/ethnicity, income, smoking, glycemic control, diabetes duration, creatinine levels, congestive heart failure, and use of other diabetes medications, the hazard ratio (HR) for each cancer associated with ever use of pioglitazone ranged from 0.7 to 1.3, with all 95% CIs including 1.0. There was a suggestion of an increased risk of melanoma (HR 1.3 [95% CI 0.9–2.0]) and NHL (1.3 [1.0–1.8]) and a decreased risk of kidney/renal pelvis cancers (0.7 [0.4–1.1]) associated with ever use of pioglitazone. These associations were unaltered with increasing dose, duration, or time since first use.

CONCLUSIONS—We found no clear evidence of an association between use of pioglitazone and risk of the incident cancers examined. Because the maximum duration of follow-up was fewer than 6 years after the initiation of pioglitazone, longer-term studies are needed.

Diabetes Care 34:923–929, 2011

undertake an epidemiologic study of pioglitazone use and the risk of cancer at several sites. The authors of this article developed the study protocol, which was approved by the European Medicines Agency. Because we were already conducting a study of pioglitazone use and bladder cancer risk, the aim of this study was to explore whether pioglitazone treatment is associated with the risk of incident cancer at the 10 sites, excluding the bladder, with the highest incidence in the U.S.: prostate, female breast, lung/bronchus, endometrial, colon, non-Hodgkin lymphoma (NHL), pancreas, kidney/renal pelvis, rectal, and melanoma.

RESEARCH DESIGN AND METHODS

RESEARCH DESIGN AND METHODS—The source population was identified from the Kaiser Permanente Northern California (KPNC) Diabetes Registry (18,19), which identifies patients from four data sources: primary hospital discharge diagnoses of diabetes, two or more outpatient visit diagnoses of diabetes, any prescription for a diabetes-

Diabetes, Obesity and Metabolism 18: 266–273, 2016.

Ten-year observational follow-up of PROactive: a randomized cardiovascular outcomes trial evaluating pioglitazone in type 2 diabetes

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	Observational follow-up only (mean 7.8 years)			Double-blind period + 10-year observational follow-up (mean 10.7 years)		
	Pioglitazone (n = 1820)	Placebo (n = 1779)	RR (95%CI) (pioglitazone versus placebo)	Pioglitazone (N = 2605)	Placebo (N = 2633)	RR (95%CI) (pioglitazone versus placebo)
Any malignancy	235 (12.9)	234 (13.2)	0.98 (0.83–1.16)	326 (12.5)	322 (12.2)	1.02 (0.89–1.18)
Adrenal	2 (0.1)	0	N/A	3 (0.1)	0	N/A
Biliary	4 (0.2)	1 (0.1)	3.91 (0.44–34.95)	5 (0.2)	3 (0.1)	1.68 (0.40–7.04)
Brain	2 (0.1)	8 (0.4)	0.24 (0.05–1.15)	3 (0.1)	11 (0.4)	0.28 (0.08–0.99)
Bladder	14 (0.8)	21 (1.2)	0.65 (0.33–1.28)	27 (1.0)	26 (1.0)	1.05 (0.61–1.79)
Breast	13 (2.1)	11 (1.8)	1.17 (0.53–2.59)*†	15 (1.7)	2 (0.8)	0.71 (0.37–1.36)*†
Cervix	1 (0.2)	2 (0.3)	0.50 (0.05–5.45)*	1 (0.1)	2 (0.2)	0.52 (0.05–5.73)*
Colon/rectal	34 (1.9)	30 (1.7)	1.11 (0.68–1.80)	49 (1.9)	45 (1.7)	1.10 (0.74–1.64)
Gastric	12 (0.7)	13 (0.7)	0.90 (0.41–1.97)	17 (0.7)	19 (0.7)	0.90 (0.47–1.74)
Haematological	18 (1.0)	12 (0.7)	1.47 (0.71–3.03)	24 (0.9)	22 (0.8)	1.10 (0.62–1.96)
Hepatic	6 (0.3)	5 (0.3)	1.17 (0.36–3.84)	6 (0.2)	5 (0.2)	1.21 (0.37–3.97)
Lung	33 (1.8)	43 (2.4)	0.75 (0.48–1.18)	48 (1.8)	55 (2.1)	0.88 (0.60–1.29)
Mesotheliomia	0	0	N/A	2 (0.1)	1 (<0.1)	2.02 (0.18–22.28)
Metastases	7 (0.4)	6 (0.3)	1.14 (0.38–3.39)	12 (0.5)	11 (0.4)	1.10 (0.49–2.49)
Oesophageal	2 (0.1)	2 (0.1)	0.98 (0.14–6.93)	2 (0.1)	2 (0.1)	1.01 (0.14–7.17)
Oropharyngeal	4 (0.2)	6 (0.3)	0.65 (0.18–2.31)	5 (0.2)	8 (0.3)	0.63 (0.21–1.93)
Ovarian/uterine	6 (0.9)	5 (0.8)	1.19 (0.36–3.87)*	10 (1.1)	10 (1.1)	1.04 (0.44–2.49)*
Pancreas	7 (0.4)	11 (0.6)	0.62 (0.24–1.60)	15 (0.6)	17 (0.6)	0.89 (0.45–1.78)
Prostate	44 (3.7)	29 (2.5)	1.47 (0.93–2.34)‡	58 (3.3)	35 (2.0)	1.59 (1.04–2.41)‡
Renal	10 (0.5)	10 (0.6)	0.98 (0.41–2.34)	13 (0.5)	17 (0.6)	0.77 (0.38–1.59)
Skin	29 (1.6)	33 (1.9)	0.86 (0.52–1.41)	35 (1.3)	36 (1.4)	0.98 (0.62–1.50)
Other	5 (0.3)	8 (0.4)	0.61 (0.20–1.86)	6 (0.2)	10 (0.4)	0.61 (0.22–1.67)

CI, confidence interval; N/A, not available; RR, relative risk.
*Calculated using only female patients.
†Excludes two cases of breast cancer in male patients in the pioglitazone group. When both male and female patients were included in the analysis, the RRs were 1.14 (0.53–2.46) for the 10-year observational period and 0.70 (0.37–1.33) for the combined period.
‡Calculated using only male patients.

DİĞER İLAÇLAR

- Akarboz
  - Artmış böbrek, azalmış akciğer, gastrik, hepatik
- Na-glukoz cotransporter inhibitörleri
  - Kardiyovaskuler sonlanım çalışmaları devam ediyor
- Glp-1 analogları, DPP-IV inhibitörleri
  - Pankreas, Tiroid

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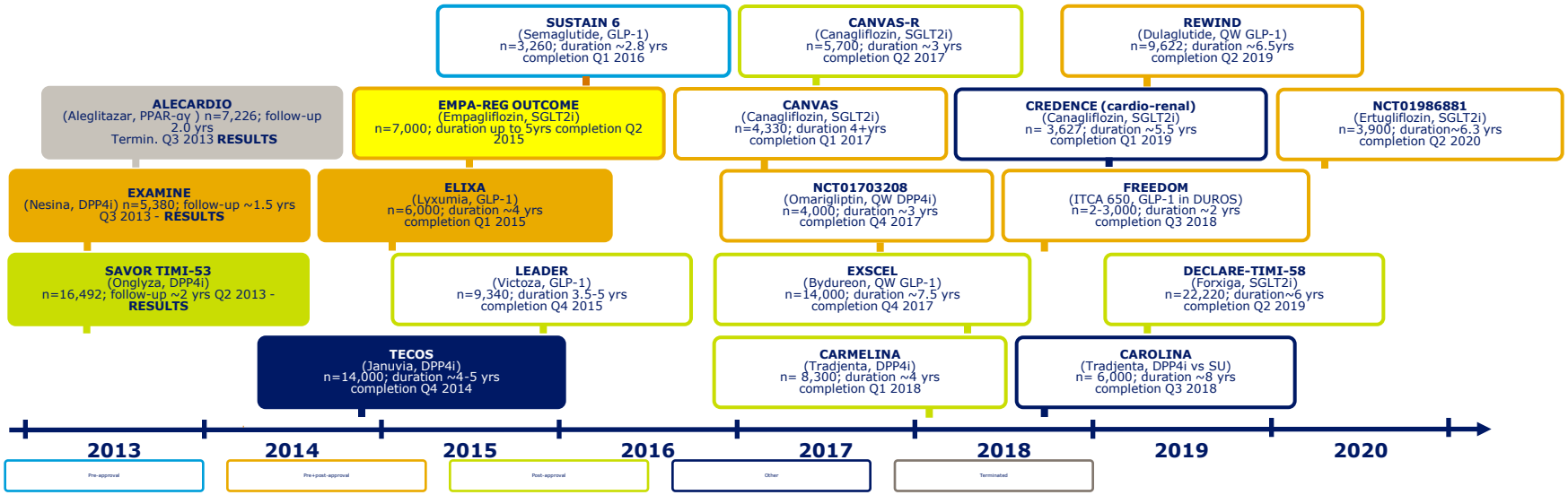

Source: ClinicalTrials.gov (April 2014). 'Completion date' is the estimated completion date for the primary outcomes measure
CVOT, cardiovascular outcomes trial; DPP4i; dipeptidyl peptidase 4 inhibitor; GLP-1, glucagon-like peptide 1; SU, sulphonylurea
McMurray JJ et al, *Lancet Diabetes Endocrinol* 2014;2:843–51

Original Investigation

Effect of Aleglitazar on Cardiovascular Outcomes After Acute Coronary Syndrome in Patients With Type 2 Diabetes Mellitus
The AleCardio Randomized Clinical Trial

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IMPORTANCE No therapy directed against diabetes has been shown to unequivocally reduce the excess risk of cardiovascular complications. Aleglitazar is a dual agonist of peroxisome proliferator-activated receptors with insulin-sensitizing and glucose-lowering actions and favorable effects on lipid profiles.

OBJECTIVE To determine whether the addition of aleglitazar to standard medical therapy reduces cardiovascular morbidity and mortality among patients with type 2 diabetes mellitus and a recent acute coronary syndrome (ACS).

DESIGN, SETTING, AND PARTICIPANTS AleCardio was a phase 3, multicenter, randomized, double-blind, placebo-controlled trial conducted in 720 hospitals in 26 countries throughout North America, Latin America, Europe, and Asia-Pacific regions. The enrollment of 7226 patients hospitalized for ACS (myocardial infarction or unstable angina) with type 2 diabetes occurred between February 2010 and May 2012; treatment was planned to continue until patients were followed-up for at least 2.5 years and 950 primary end point events were positively adjudicated.

INTERVENTIONS Randomized in a 1:1 ratio to receive aleglitazar 150 µg or placebo daily.

MAIN OUTCOMES AND MEASURES The primary efficacy end point was time to cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke. Principal safety end points were hospitalization due to heart failure and changes in renal function.

RESULTS The trial was terminated on July 2, 2013, after a median follow-up of 104 weeks, upon recommendation of the data and safety monitoring board due to futility for efficacy at an unplanned interim analysis and increased rates of safety end points. A total of 3.1% of patients were lost to follow-up and 3.2% of patients withdrew consent. The primary end point occurred in 344 patients (9.5%) in the aleglitazar group and 360 patients (10.0%) in the placebo group (hazard ratio, 0.96 [95% CI, 0.83-1.11]; $P = .57$). Rates of serious adverse events, including heart failure (3.4% for aleglitazar vs 2.8% for placebo, $P = .14$), gastrointestinal hemorrhages (2.4% for aleglitazar vs 1.7% for placebo, $P = .03$), and renal dysfunction (7.4% for aleglitazar vs 2.7% for placebo, $P < .001$) were increased.

CONCLUSIONS AND RELEVANCE Among patients with type 2 diabetes and recent ACS, use of aleglitazar did not reduce the risk of cardiovascular outcomes. These findings do not support the use of aleglitazar in this setting with a goal of reducing cardiovascular risk.

TRIAL REGISTRATION clinicaltrials.gov Identifier: NCT01042769

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Pancreatitis, Pancreatic, and Thyroid Cancer With Glucagon-Like Peptide-1–Based Therapies

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İnkretin Bazlı Tedaviler ve Pankreas Kanseri

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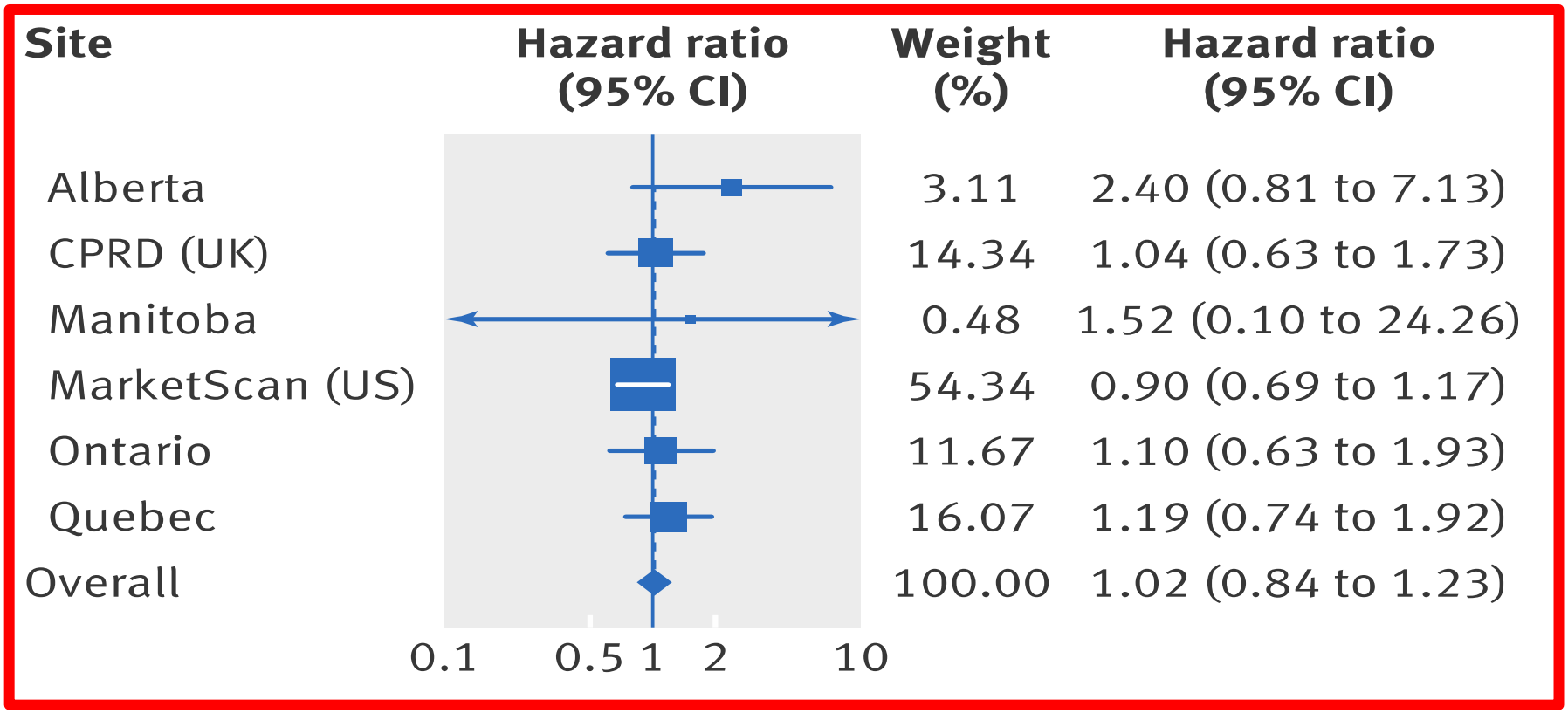

BMJ 2016;352:i581 | doi: 10.1136/bmj.i581

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Saxagliptin and Cardiovascular Outcomes in Patients with Type 2 Diabetes Mellitus

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ABSTRACT

BACKGROUND

The cardiovascular safety and efficacy of many current antihyperglycemic agents, including saxagliptin, a dipeptidyl peptidase 4 (DPP-4) inhibitor, are unclear.

METHODS

We randomly assigned 16,492 patients with type 2 diabetes who had a history of, or were at risk for, cardiovascular events to receive saxagliptin or placebo and followed them for a median of 2.1 years. Physicians were permitted to adjust other medications, including antihyperglycemic agents. The primary end point was a composite of cardiovascular death, myocardial infarction, or ischemic stroke.

RESULTS

A primary end-point event occurred in 613 patients in the saxagliptin group and in 609 patients in the placebo group (7.3% and 7.2%, respectively, according to 2-year Kaplan–Meier estimates; hazard ratio with saxagliptin, 1.00; 95% confidence interval [CI], 0.89 to 1.12; P=0.99 for superiority; P<0.001 for noninferiority); the results were similar in the "on-treatment" analysis (hazard ratio, 1.03; 95% CI, 0.91 to 1.17). The major secondary end point of a composite of cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina, coronary revascularization, or heart failure occurred in 1059 patients in the saxagliptin group and in 1034 patients in the placebo group (12.8% and 12.4%, respectively, according to 2-year Kaplan–Meier estimates; hazard ratio, 1.02; 95% CI, 0.94 to 1.11; P=0.66). More patients in the saxagliptin group than in the placebo group were hospitalized for heart failure (3.5% vs. 2.8%; hazard ratio, 1.27; 95% CI, 1.07 to 1.51; P=0.007). Rates of adjudicated cases of acute and chronic pancreatitis were similar in the two groups (acute pancreatitis, 0.3% in the saxagliptin group and 0.2% in the placebo group; chronic pancreatitis, <0.1% and 0.1% in the two groups, respectively).

CONCLUSIONS

DPP-4 inhibition with saxagliptin did not increase or decrease the rate of ischemic events, though the rate of hospitalization for heart failure was increased. Although saxagliptin improves glycemic control, other approaches are necessary to reduce cardiovascular risk in patients with diabetes. (Funded by AstraZeneca and Bristol-Myers Squibb; SAVOR-TIMI 53 ClinicalTrials.gov number, NCT01107886.)

Table 3. Safety End Points.

End Point	Saxagliptin (N=8280)	Placebo (N=8212)	P Value*
	no. (%)		
Thrombocytopenia	55 (0.7)	65 (0.8)	0.36
Lymphocytopenia	49 (0.6)	40 (0.5)	0.40
Severe infection	590 (7.1)	576 (7.0)	0.78
Opportunistic infection	21 (0.3)	35 (0.4)	0.06
Hypersensitivity reaction	93 (1.1)	89 (1.1)	0.82
Bone fracture	241 (2.9)	240 (2.9)	1.00
Skin reaction	228 (2.8)	232 (2.8)	0.81
Renal abnormality	483 (5.8)	418 (5.1)	0.04
Any hypoglycemia†	1264 (15.3)	1104 (13.4)	<0.001
Major	177 (2.1)	140 (1.7)	0.047
Minor	1172 (14.2)	1028 (12.5)	0.002
Cancer	327 (3.9)	362 (4.4)	0.15
Any liver abnormality†	55 (0.7)	67 (0.8)	0.28
AST >3× ULN	60 (0.7)	61 (0.7)	0.93
AST >10× ULN	12 (0.1)	15 (0.2)	0.57
ALT or AST >3× ULN and total bilirubin >2× ULN	13 (0.2)	23 (0.3)	0.097
Any pancreatitis†	24 (0.3)	21 (0.3)	0.77
Acute: definite or possible	22 (0.3)	16 (0.2)	0.42
Acute: definite	17 (0.2)	9 (0.1)	0.17
Acute: possible	6 (0.1)	7 (0.1)	0.79
Chronic	2 (<0.1)	6 (0.1)	0.18

* P values were calculated with the use of Fisher's exact test. ALT denotes alanine aminotransferase, AST aspartate aminotransferase, and ULN upper limit of the normal range.

† Patients may have had more than one type of event.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Alogliptin after Acute Coronary Syndrome in Patients with Type 2 Diabetes

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ABSTRACT

BACKGROUND

To assess potentially elevated cardiovascular risk related to new antihyperglycemic drugs in patients with type 2 diabetes, regulatory agencies require a comprehensive evaluation of the cardiovascular safety profile of new antidiabetic therapies. We assessed cardiovascular outcomes with alogliptin, a new inhibitor of dipeptidyl peptidase 4 (DPP-4), as compared with placebo in patients with type 2 diabetes who had had a recent acute coronary syndrome.

METHODS

We randomly assigned patients with type 2 diabetes and either an acute myocardial infarction or unstable angina requiring hospitalization within the previous 15 to 90 days to receive alogliptin or placebo in addition to existing antihyperglycemic and cardiovascular drug therapy. The study design was a double-blind, noninferiority trial with a prespecified noninferiority margin of 1.3 for the hazard ratio for the primary end point of a composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke.

RESULTS

A total of 5380 patients underwent randomization and were followed for up to 40 months (median, 18 months). A primary end-point event occurred in 305 patients assigned to alogliptin (11.3%) and in 316 patients assigned to placebo (11.8%) (hazard ratio, 0.96; upper boundary of the one-sided repeated confidence interval, 1.16; $P<0.001$ for noninferiority). Glycated hemoglobin levels were significantly lower with alogliptin than with placebo (mean difference, −0.36 percentage points; $P<0.001$). Incidences of hypoglycemia, cancer, pancreatitis, and initiation of dialysis were similar with alogliptin and placebo.

CONCLUSIONS

Among patients with type 2 diabetes who had had a recent acute coronary syndrome, the rates of major adverse cardiovascular events were not increased with the DPP-4 inhibitor alogliptin as compared with placebo. (Funded by Takeda Development Center Americas; EXAMINE ClinicalTrials.gov number, NCT00968708.)

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*A full list of investigators for the Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care (EXAMINE) study is provided in the Supplementary Appendix, available at NEJM.org.

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Supplementary Table 2. Other Safety End Points			
	Placebo (n=2679)	Alogliptin (n=2701)	P value*
Any Serious Adverse Event,	952 (35.5)	907 (33.6)	0.14
Serious hypoglycemia**	16 (0.6)	18 (0.7)	0.86
Any Adverse Event	2111 (78.8)	2160 (80.0)	0.30
Any hypoglycemia **	173 (6.5)	181 (6.7)	0.74
Pancreatitis†			
Acute	8 (0.3)	12 (0.4)	0.50
Chronic	4 (0.1)	5 (0.2)	1.00
Angioedema	13 (0.5)	17 (0.6)	0.58
Malignancy	51 (1.9)	55 (2.0)	0.77
Renal dialysis	22 (0.8)	24 (0.9)	0.88
Laboratory Results			
Serum aminotransferases >3 times upper limit of normal at any time during trial			
Alanine aminotransferase‡	46 (1.7)	64 (2.4)	0.10
Aspartate aminotransferase§	43 (1.6)	48 (1.8)	0.67

*P values were calculated by Fisher's exact test with no adjustment for multiple comparisons; **hypoglycemia was reported by site investigators; †terms included pancreatitis acute, relapsing pancreatitis, and pancreatitis; ‡The upper limit of normal for the alanine aminotransferase was 25 U/L. §The upper limit of normal for aspartate aminotransferase was 22 U/L

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Lixisenatide in Patients with Type 2 Diabetes and Acute Coronary Syndrome

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ABSTRACT

BACKGROUND

Cardiovascular morbidity and mortality are higher among patients with type 2 diabetes, particularly those with concomitant cardiovascular diseases, than in most other populations. We assessed the effects of lixisenatide, a glucagon-like peptide 1–receptor agonist, on cardiovascular outcomes in patients with type 2 diabetes who had had a recent acute coronary event.

METHODS

We randomly assigned patients with type 2 diabetes who had had a myocardial infarction or who had been hospitalized for unstable angina within the previous 180 days to receive lixisenatide or placebo in addition to locally determined standards of care. The trial was designed with adequate statistical power to assess whether lixisenatide was noninferior as well as superior to placebo, as defined by an upper boundary of the 95% confidence interval for the hazard ratio of less than 1.3 and 1.0, respectively, for the primary composite end point of cardiovascular death, myocardial infarction, stroke, or hospitalization for unstable angina.

RESULTS

The 6068 patients who underwent randomization were followed for a median of 25 months. A primary end-point event occurred in 406 patients (13.4%) in the lixisenatide group and in 399 (13.2%) in the placebo group (hazard ratio, 1.02; 95% confidence interval [CI], 0.89 to 1.17), which showed the noninferiority of lixisenatide to placebo ($P<0.001$) but did not show superiority ($P=0.81$). There were no significant between-group differences in the rate of hospitalization for heart failure (hazard ratio in the lixisenatide group, 0.96; 95% CI, 0.75 to 1.23) or the rate of death (hazard ratio, 0.94; 95% CI, 0.78 to 1.13). Lixisenatide was not associated with a higher rate of serious adverse events or severe hypoglycemia, pancreatitis, pancreatic neoplasms, or allergic reactions than was placebo.

CONCLUSIONS

In patients with type 2 diabetes and a recent acute coronary syndrome, the addition of lixisenatide to usual care did not significantly alter the rate of major cardiovascular events or other serious adverse events. (Funded by Sanofi; ELIXA ClinicalTrials.gov number, NCT01147250.)

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*A list of the investigators and committee members in the Evaluation of Lixisenatide in Acute Coronary Syndrome (ELIXA) trial is provided in the Supplementary Appendix, available at NEJM.org.

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Table 3. Serious Adverse Events.*

Event	Placebo (N = 3032)	Lixisenatide (N = 3031)
	no. of patients with event (%)	
Any event	669 (22.1)	625 (20.6)
Blood or lymphatic event	14 (0.5)	14 (0.5)
Cardiac event†	107 (3.5)	83 (2.7)
Ear or labyrinth event	4 (0.1)	5 (0.2)
Endocrine event	3 (0.1)	2 (0.1)
Eye event	13 (0.4)	9 (0.3)
Gastrointestinal event	81 (2.7)	66 (2.2)
General event	58 (1.9)	64 (2.1)
Hepatobiliary event	28 (0.9)	36 (1.2)
Immune system event	2 (0.1)	4 (0.1)
Infection	186 (6.1)	173 (5.7)
Injury or poisoning	50 (1.6)	44 (1.5)
Investigations‡	19 (0.6)	10 (0.3)
Metabolism or nutrition event	57 (1.9)	33 (1.1)
Musculoskeletal event	35 (1.2)	32 (1.1)
Neoplasm	61 (2.0)	72 (2.4)
Nervous system event	53 (1.7)	47 (1.6)
Psychiatric event	5 (0.2)	9 (0.3)
Renal or urinary event	48 (1.6)	48 (1.6)
Reproductive system event	5 (0.2)	13 (0.4)
Respiratory or thoracic event	58 (1.9)	58 (1.9)
Skin or subcutaneous tissue event	18 (0.6)	14 (0.5)
Social circumstances	0	1 (<0.1)
Surgical or medical procedure	6 (0.2)	6 (0.2)
Vascular event	71 (2.3)	59 (1.9)

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Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes

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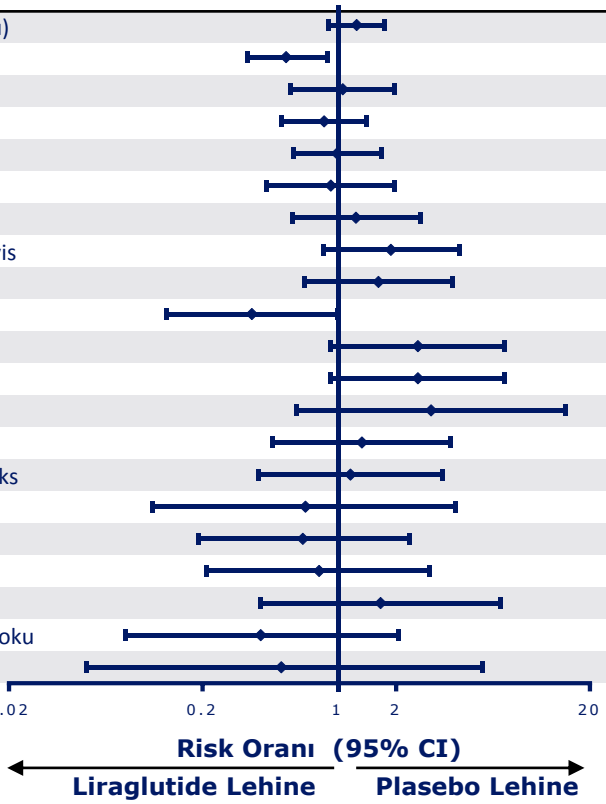

	Risk Oranı (95% CI)	Lira N	Lira %	Plasebo N	Plasebo %
Cilt (melanom dışı)	1.25 (0.90 ; 1.75)	78	1.7	62	1.3
Prostat	0.54 (0.34 ; 0.88)	26	0.9	47	1.6
Meme	1.06 (0.57 ; 1.96)	21	1.3	20	1.2
Akciğer/Bronş	0.85 (0.51 ; 1.40)	28	0.6	33	0.7
Kolorektal	0.99 (0.59 ; 1.68)	28	0.6	28	0.6
Diğer	0.92 (0.43 ; 1.97)	13	0.3	14	0.3
Mesane	1.24 (0.58 ; 2.66)	15	0.3	12	0.3
Böbrek/renal pelvis	1.88 (0.84 ; 4.22)	17	0.4	9	0.2
Hepatik/biliyer	1.62 (0.67 ; 3.90)	13	0.3	8	0.2
Lösemiler	0.36 (0.13 ; 0.99)	5	0.1	14	0.3
Pankreatik	2.59 (0.92 ; 7.27)	13	0.3	5	0.1
Cilt (melanoma)	2.59 (0.92 ; 7.27)	13	0.3	5	0.1
Servikal / vajinal	3.03 (0.61 ; 15.0)	6	0.4	2	0.1
Lenfoma	1.33 (0.46 ; 3.82)	8	0.2	6	0.1
Oral kavite /farenks	1.16 (0.39 ; 3.46)	7	0.1	6	0.1
Üterin	0.68 (0.11 ; 4.05)	2	0.1	3	0.2
Eosofageal	0.66 (0.19 ; 2.34)	4	0.1	6	0.1
Gastrik	0.80 (0.21 ; 2.97)	4	0.1	5	0.1
Tiroid	1.66 (0.40 ; 6.95)	5	0.1	3	0.1
Kemik/YumuşakDoku	0.40 (0.08 ; 2.05)	2	0.0	5	0.1
Ovaryen	0.51 (0.05 ; 5.58)	1	0.1	2	0.1

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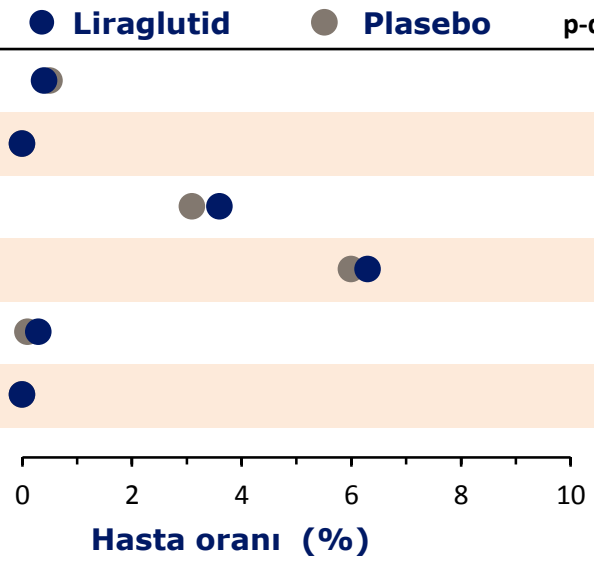
Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes

Steven P. Marso, M.D., Gilbert H. Daniels, M.D., Kirstine Brown-Frandsen, M.D., Peter Kristensen, M.D., E.M.B.A., Johannes F.E. Mann, M.D., Michael A. Nauck, M.D., Steven E. Nissen, M.D., Stuart Pocock, Ph.D., Neil R. Poulter, F.Med.Sci., Lasse S. Ravn, M.D., Ph.D., William M. Steinberg, M.D., Mette Stockner, M.D., Bernard Zinman, M.D., Richard M. Bergenstal, M.D., and John B. Buse, M.D., Ph.D., for the LEADER Steering Committee on behalf of the LEADER Trial Investigators*

Pankreatit ve neoplazmlar (karar verilmiş)

	Liraglutid		Plasebo		
	N	%	N	%	p-değeri
Akut pankreatit	18	0.4	23	0.5	0.44
Kronik pankreatit	0	0	2	<0.1	0.16
Herhangi bir benign neoplazm	168	3.6	145	3.1	0.18
Herhangi bir malign neoplazm	296	6.3	279	6.0	0.46
Pankreatik karsinom	13	0.3	5	0.1	0.06
Medüller tiroid karsinomu	0	0	1	<0.1	0.32



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Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes

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Table S5. Additional pancreatic cancer data (number of subjects with an event).

	Liraglutide	Placebo
Neoplasm adjudication	13	5
Neoplasm + death adjudication	13	9
MedDRA search in AE database (not adjudicated)	11	10

Analysis of pancreatic cancer was established using a 3-step independent process. First, all neoplasms were adjudicated by the Event Adjudication Committee (EAC), foremost by histology or cytology, to establish a tissue of origin. Eighteen neoplasms with the tissue of origin "pancreas" were identified by the EAC, 13 in the liraglutide group and 5 in the placebo group. Second, all deaths were adjudicated, with a diagnosis provided for all confirmed non-cardiovascular deaths using less stringent criteria, i.e., not requiring a pathological diagnosis for neoplasms. In this step, another four deaths were adjudicated as from malignancy related to pancreatic cancer, all in the placebo group. Third, based on investigator reports of adverse events and use of MedDRA SMQ search criteria, 21 subjects with pancreatic cancer were identified: 11 in the liraglutide group and 10 in the placebo group.

ORIGINAL ARTICLE

Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes

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ABSTRACT

BACKGROUND

Regulatory guidance specifies the need to establish cardiovascular safety of new diabetes therapies in patients with type 2 diabetes in order to rule out excess cardiovascular risk. The cardiovascular effects of semaglutide, a glucagon-like peptide 1 analogue with an extended half-life of approximately 1 week, in type 2 diabetes are unknown.

METHODS

We randomly assigned 3297 patients with type 2 diabetes who were on a standard-care regimen to receive once-weekly semaglutide (0.5 mg or 1.0 mg) or placebo for 104 weeks. The primary composite outcome was the first occurrence of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke. We hypothesized that semaglutide would be noninferior to placebo for the primary outcome. The noninferiority margin was 1.8 for the upper boundary of the 95% confidence interval of the hazard ratio.

Table 3. Selected Adverse Events.*

Event	Semaglutide		Placebo	
	0.5 mg (N=826)	1.0 mg (N=822)	0.5 mg (N=824)	1.0 mg (N=825)
	number of patients (percent)			
Adverse event	740 (89.6)	732 (89.1)	748 (90.8)	736 (89.2)
Serious adverse event†	289 (35.0)	276 (33.6)	329 (39.9)	298 (36.1)
Severe adverse event‡	200 (24.2)	207 (25.2)	216 (26.2)	194 (23.5)
Adverse event leading to treatment discontinuation	95 (11.5)	119 (14.5)	47 (5.7)	63 (7.6)
Nausea	18 (2.2)	38 (4.6)	2 (0.2)	2 (0.2)
Vomiting	14 (1.7)	23 (2.8)	3 (0.4)	2 (0.2)
Diarrhea	15 (1.8)	19 (2.3)	5 (0.6)	2 (0.2)
Gastrointestinal disorder§	419 (50.7)	430 (52.3)	294 (35.7)	290 (35.2)
Diarrhea	148 (17.9)	151 (18.4)	98 (11.9)	87 (10.5)
Nausea	143 (17.3)	180 (21.9)	62 (7.5)	67 (8.1)
Vomiting	87 (10.5)	122 (14.8)	43 (5.2)	34 (4.1)
Cardiac disorder§	173 (20.9)	150 (18.2)	189 (22.9)	173 (21.0)
Atrial fibrillation	27 (3.3)	23 (2.8)	32 (3.9)	26 (3.2)
Acute pancreatitis¶	6 (0.7)	3 (0.4)	3 (0.4)	9 (1.1)
Gallbladder disorder‖	32 (3.9)	26 (3.2)	38 (4.6)	23 (2.8)
Cholelithiasis	21 (2.5)	17 (2.1)	19 (2.3)	12 (1.5)
Acute cholecystitis	4 (0.5)	0	6 (0.7)	2 (0.2)
Severe or symptomatic hypoglycemic event**	191 (23.1)	178 (21.7)	177 (21.5)	173 (21.0)
Acute renal failure‖	42 (5.1)	23 (2.8)	34 (4.1)	35 (4.2)
Allergic reaction‖	49 (5.9)	49 (6.0)	46 (5.6)	57 (6.9)
Injection-site reaction‖	8 (1.0)	9 (1.1)	9 (1.1)	12 (1.5)
Neoplasm¶	66 (8.0)	89 (10.8)	70 (8.5)	69 (8.4)
Benign	40 (4.8)	54 (6.6)	36 (4.4)	34 (4.1)
Premalignant	4 (0.5)	6 (0.7)	3 (0.4)	2 (0.2)
Malignant				
Any	26 (3.1)	40 (4.9)	35 (4.2)	35 (4.2)
Pancreatic	0	1 (0.1)	2 (0.2)	2 (0.2)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes

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ABSTRACT

BACKGROUND

The effects of empagliflozin, an inhibitor of sodium–glucose cotransporter 2, in addition to standard care, on cardiovascular morbidity and mortality in patients with type 2 diabetes at high cardiovascular risk are not known.

METHODS

We randomly assigned patients to receive 10 mg or 25 mg of empagliflozin or placebo once daily. The primary composite outcome was death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke, as analyzed in the pooled empagliflozin group versus the placebo group. The key secondary composite outcome was the primary outcome plus hospitalization for unstable angina.

RESULTS

A total of 7020 patients were treated (median observation time, 3.1 years). The primary outcome occurred in 490 of 4687 patients (10.5%) in the pooled empagliflozin group and in 282 of 2333 patients (12.1%) in the placebo group (hazard ratio in the empagliflozin group, 0.86; 95.02% confidence interval, 0.74 to 0.99; P=0.04 for superiority). There were no significant between-group differences in the rates of myocardial infarction or stroke, but in the empagliflozin group there were significantly lower rates of death from cardiovascular causes (3.7%, vs. 5.9% in the placebo group; 38% relative risk reduction), hospitalization for heart failure (2.7% and 4.1%, respectively; 35% relative risk reduction), and death from any cause (5.7% and 8.3%, respectively; 32% relative risk reduction). There was no significant between-group difference in the key secondary outcome (P=0.08 for superiority). Among patients receiving empagliflozin, there was an increased rate of genital infection but no increase in other adverse events.

CONCLUSIONS

Patients with type 2 diabetes at high risk for cardiovascular events who received empagliflozin, as compared with placebo, had a lower rate of the primary composite cardiovascular outcome and of death from any cause when the study drug was added to standard care. (Funded by Boehringer Ingelheim and Eli Lilly; EMPA-REG OUTCOME ClinicalTrials.gov number, NCT01131676.)

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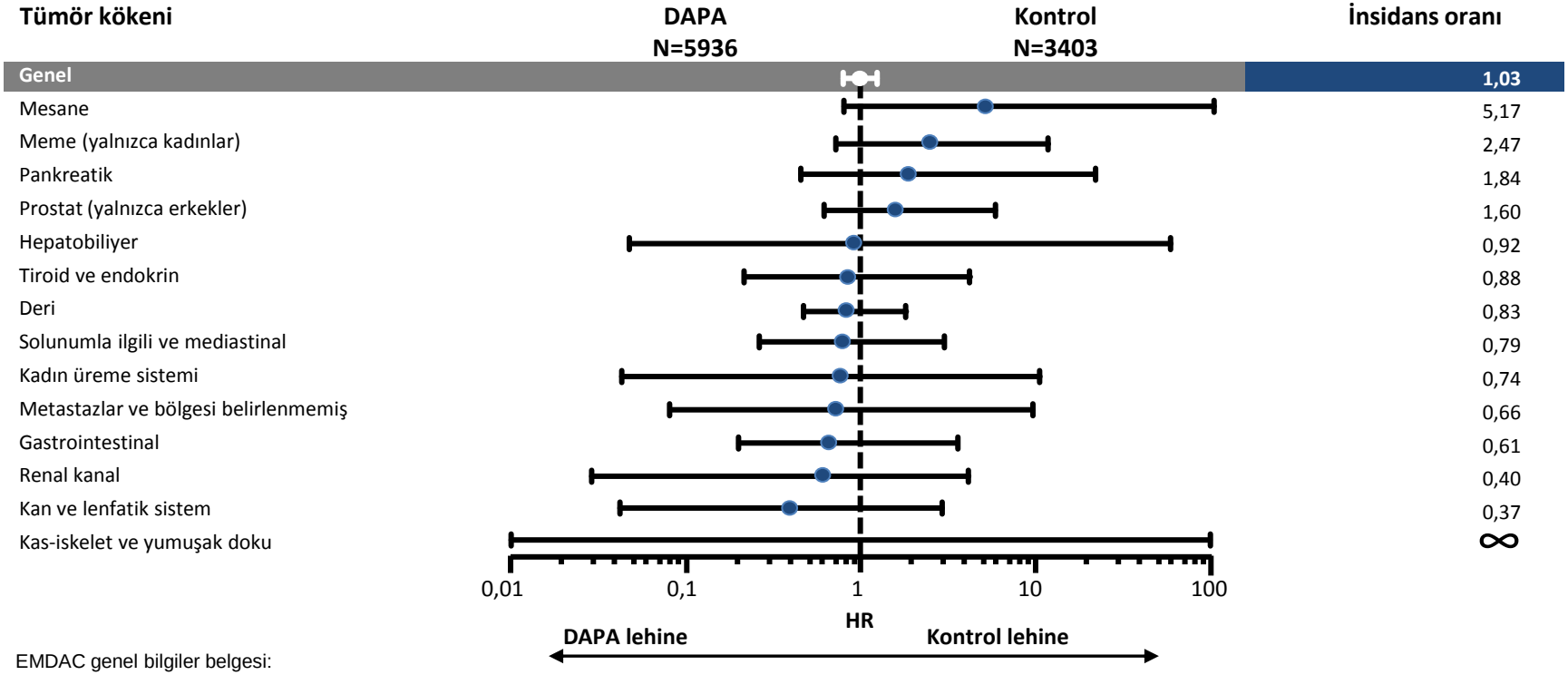
Dapagliflozin

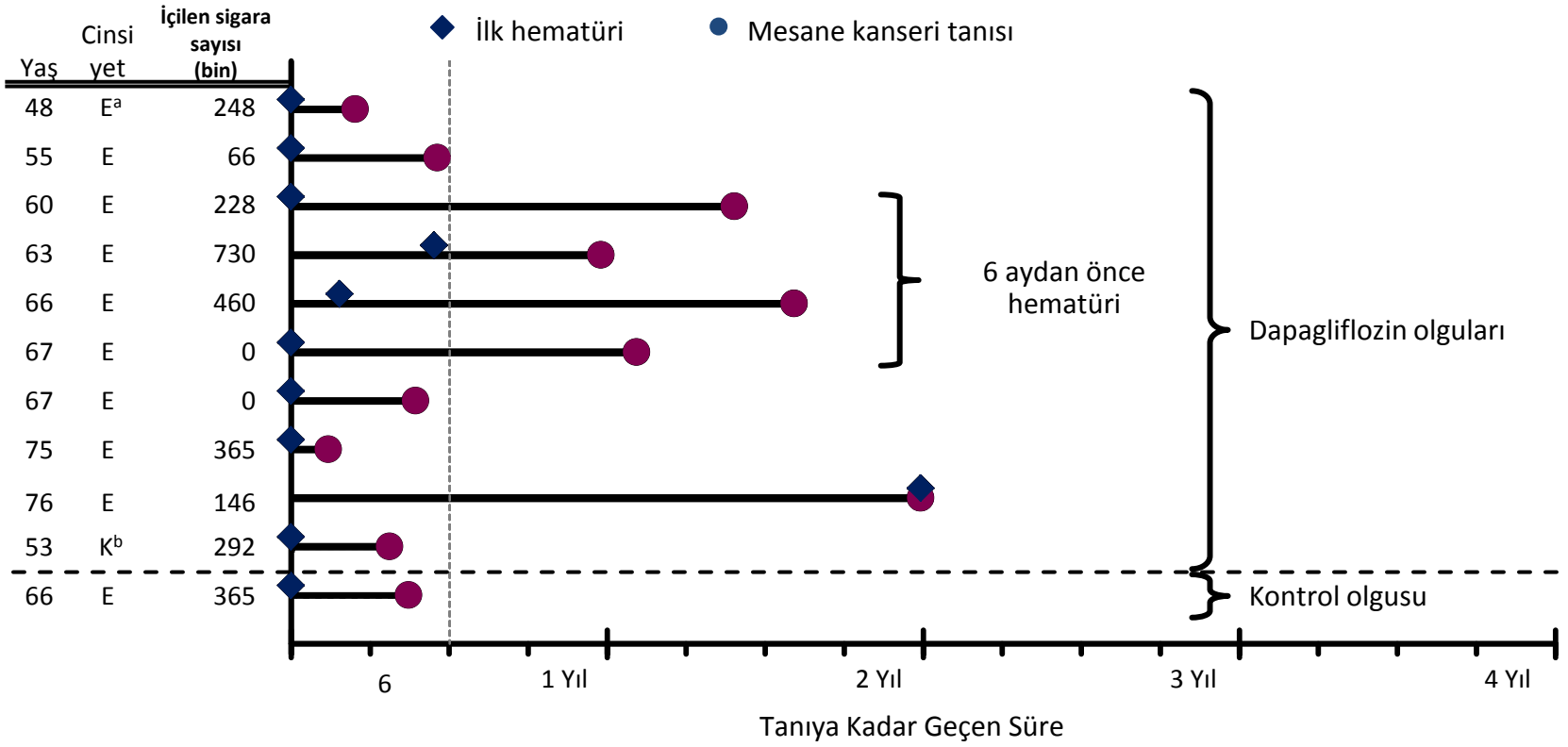
- Malignitelerde genel dengesizlik görülmemiş; farklı tümör türlerinin tanısında anlamlı olmayan dengesizlikler gözlenmiştir.

Tümör tipine göre maligniteler, birleştirilen tüm faz 2b ve 3 çalışmalar



EMDAC genel bilgiler belgesi:
www.fda.gov/downloads/advisorycommittees/committeesmeetingmaterials/drugs/endocrinologicandmetabolicdrugsadvisorycommittee/ucm378079.pdf

Dapagliflozin
Mesane Kanseri Olgularının Detaylı İncelemesi



[a]Bu olguda hematüri çalışmaya girmeden önce gözlenmiştir.
[b]Bu olgu FDA'ya tekrar başvuru için veri kesme noktası zamanında bitmemiş olan 93-005 çalışmasında tanımlanmış ve tekrar başvuru dosyasına dahil edilmemiştir.

Dapagliflozin Karsinojenik Değildir

Klinik öncesi toksikoloji verileri herhangi bir kanser sinyali göstermemektedir

- Genotoksik değil
- 2 yıllık karsinojenite çalışmalarında DAPA ile ilgili tümör saptanmamıştır
  - Tümörlerde veya preneoplastik lezyonlarda artış yok
  - Tümör latensinde kısalma yok

Mesane tümörleri ile mekanistik bağ yoktur.

- Mesanede SGLT2 ekspresyonu gerçekleşmemektedir
- Aşağıda belirtilenlerde tümör veya preneoplastik lezyonlar olmadan glukozüri:
  - Hayvan karsinojenite modelleri
  - $SGLT^{-/-}$ fareler
- Onaylı SGLT2 inhibitörü

Dapa insanda mesane kanseri büyümesini uyarmaz.

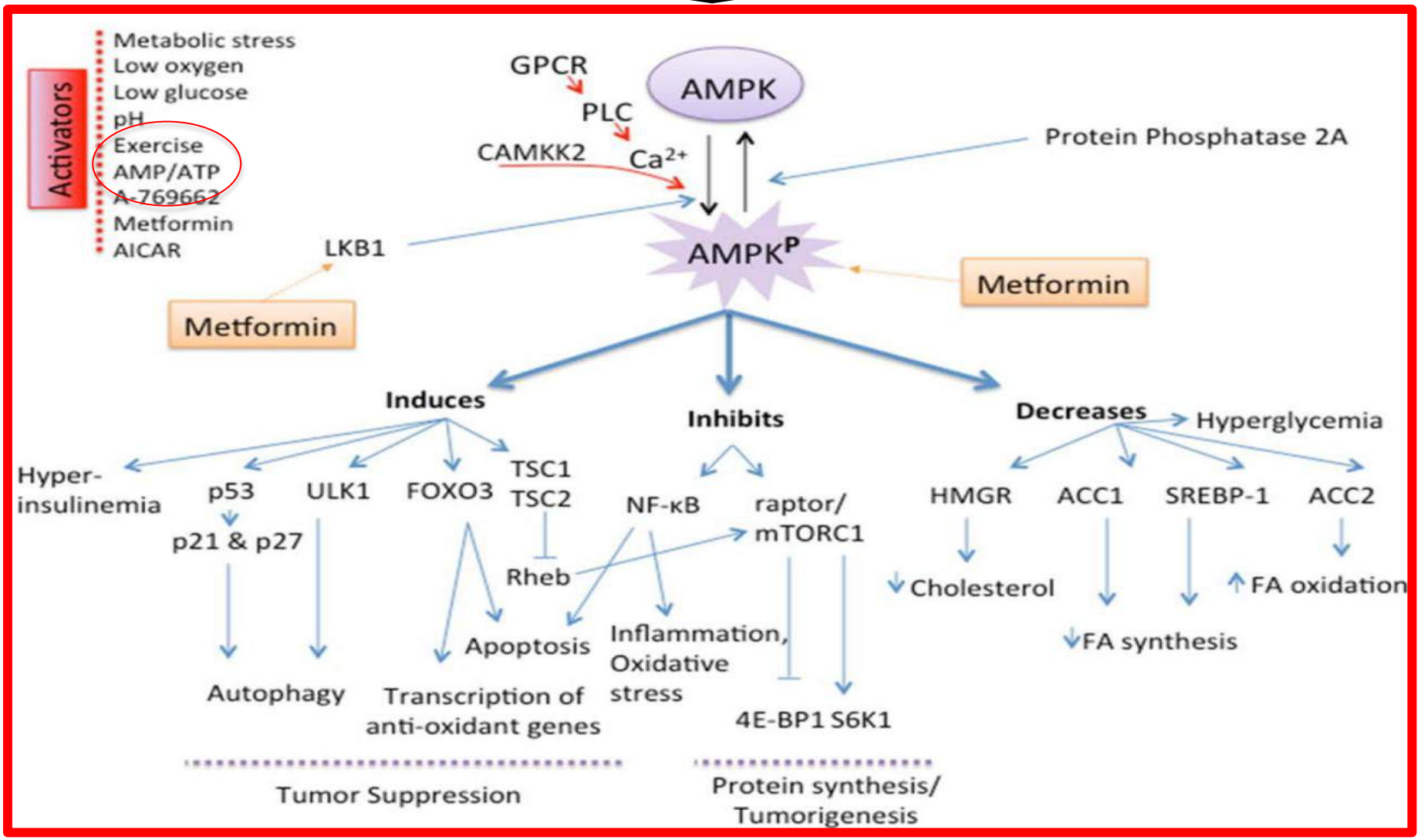
- Tamamlayıcı *in vitro* proliferasyon ve *in vivo* ksenogreft modellerinde test edilen çoklu insan mesane karsinomu geçişli hücre soyları

Glukoz insanda mesane kanseri hücrelerinin çoğalmasını uyarmaz.

- *İn vitro* ortamda test edilen çoklu insan mesane karsinomu geçişli hücre soyları
- 25-50mM glukoz konsantrasyonları (hasta idrarında gözlenenden düşük) sitostatik bulunmuştur.

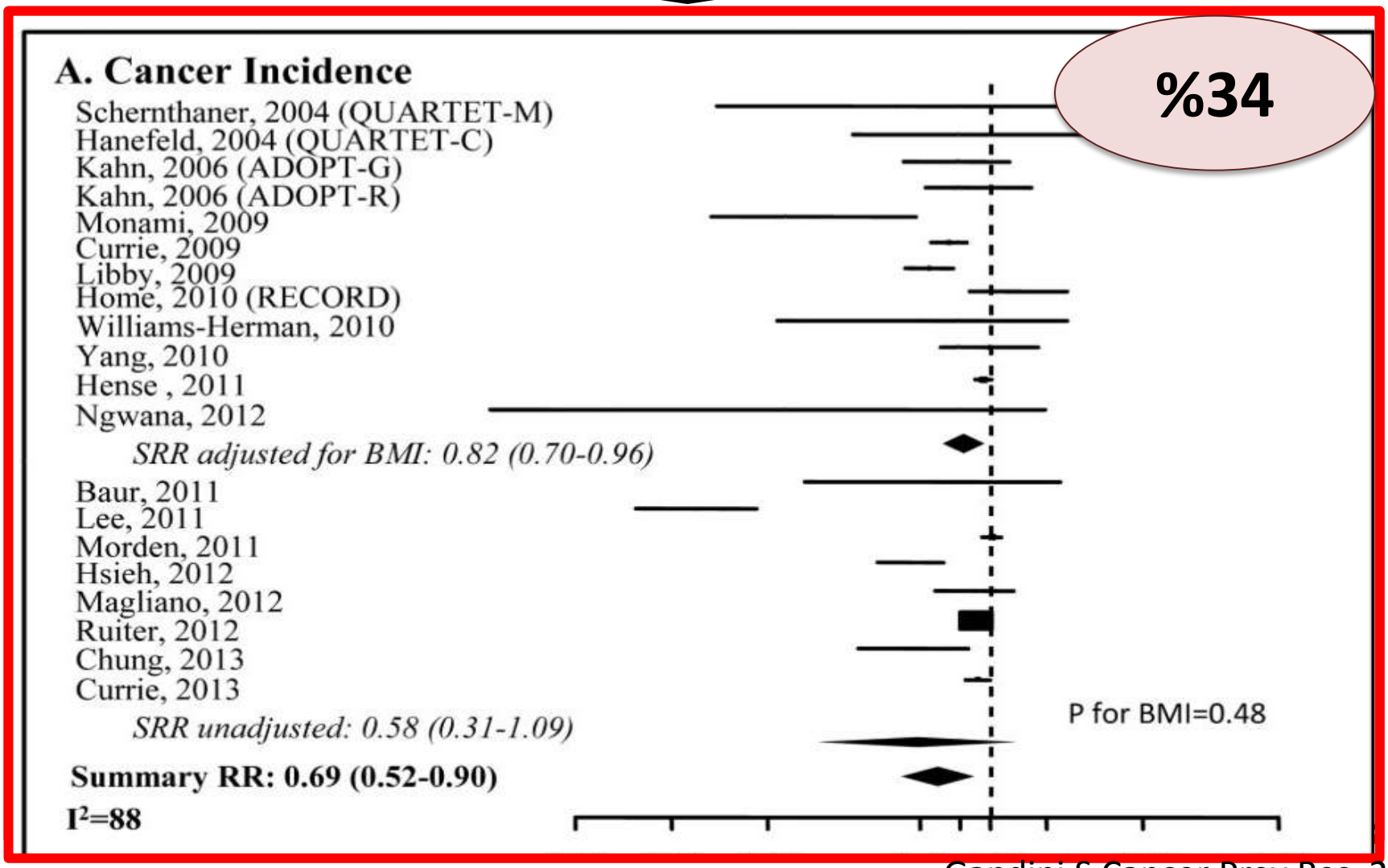
EMDAC genel bilgiler belgesi:
www.fda.gov/downloads/advisorycommittees/committeesmeetingmaterials/drugs/endocrinologicandmetabolicdrugsadvisorycommittee/ucm378079.pdf

METFORMİN & KANSER



Anwar M et alJournal of Cancer 2014

METFORMİN & KANSER



Gandini S Cancer Prev Res 2014

SON SÖZLER

- Diyabet - kanser ilişkisi birliktelik mi ? Komplikasyon mu?
- Diyabette kanser görülme riski artmakta
- Her ikisinin ortak risk faktörleri !
- İR, hiperinsülinemi, seks hormonları, adipokinler, inflamasyon, hiperglisemi
- DM kanser mortalite, morbiditeyi arttırır!!
- Obeziteye doğru yaklaşım ve tedavi kanser gelişimini ve mortaliteyi azaltabilir!!!