A Year in Endocrinology: 2014

Mark WJ Strachan

Metabolic Unit, Western General Hospital, Edinburgh

2014

2014

2014

What to Choose?

- The most cited papers?
- The most viewed papers?

- The most clinically relevant papers?
- Papers with the biggest wow factor?
- The most interesting papers?

Top 20 Read Endocrinology Articles in 2014

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1. Efficacy and safety of insulin degludec 200 u/ml and insulin degludec 100 u/ml in patients with type 2 diabetes (Begin: Compare)
   Endocrine Practice - 02/12/2014
2. High protein weight loss diets in obese subjects with type 2 diabetes mellitus
   Nutrition, Metabolism & Cardiovascular Diseases - 01/03/2014
3. Effects of low dose metformin in adolescents with type I diabetes mellitus: A randomized, double-blinded placebo-controlled study
   Pediatric Diabetes - 04/07/2014
4. Comparing dosing of basal insulin analogues detemir and glargine: Is it really unit-per-unit and dose-per-dose?
   Annals of Pharmacotherapy - 03/12/2014
5. The safety of dipeptidyl peptidase-4 (DPP-4) inhibitors or sodium-glucose cotransporter 2 (SGLT-2) inhibitors added to metformin background therapy in patients with type 2 diabetes mellitus: a systematic review and meta-analysis
   Diabetes/Metabolism Research and Reviews - 12/05/2013
6. The effect of Mediterranean diet on the development of type 2 diabetes mellitus: A meta-analysis of 10 prospective studies and 136846 participants
   Metabolism - 05/08/2014
7. Effect of large doses of parenteral vitamin D on glycaemic control and calcium/phosphate metabolism in patients with stable type 2 diabetes mellitus: A randomised, placebo-controlled, prospective pilot study
   Swiss Medical Weekly - 04/04/2014
8. Hemoglobin A1c, fasting plasma glucose, and 2-hour plasma glucose distributions in U.S. population subgroups: NHANES 2005–2010
   Annals of Epidemiology - 02/13/2014
9. Aspirin in type 2 diabetes, a randomised controlled study: effect of different doses on inflammation, oxidative stress, insulin resistance and endothelial function
   International Journal of Clinical Practice - 01/02/2014
10. The effects of green tea consumption on metabolic and anthropometric indices in patients with Type 2 diabetes
    Journal of Research in Medical Sciences - 12/23/2013
11. Effect of 25 (OH) D replacements in patients with primary hyperparathyroidism (PHPT) and coexistent vitamin D deficiency on serum 25(OH) D, calcium and PTH levels: A meta-analysis and review of literature
    Clinical Endocrinology - 01/07/2014
12. Metformin is associated with survival benefit in cancer patients with concurrent type 2 diabetes: A systematic review and meta-analysis
    The Oncologist - 12/06/2013

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   Endocrine Practice - 02/12/2014
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By Topic

- **All Topics**
  - Diabetes (324)
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  - Obesity (187)
  - Osteoporosis/ Bone Disease (151)
  - Diet/Nutrition (122)
  - Thyroid Disease (67)
  - More

By Article Category

- **All Categories**
  - Research (286)
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  - Commentary (164)
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ORIGINAL ARTICLE

Follow-up of Blood-Pressure Lowering and Glucose Control in Type 2 Diabetes

October 9, 2014 | Zoungas S., Chalmers J., Neal B., et al. | N Engl J Med 2014; 371:1392-1406

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ORIGINAL ARTICLE

Trial of the Route of Early Nutritional Support in Critically Ill Adults

October 30, 2014 | Harvey S.E., Parrott F., Harrison D.A., et al. | N Engl J Med 2014; 371:1673-1684

CME | Comments

CLINICAL IMPLICATIONS OF BASIC RESEARCH

The Target of Metformin in Type 2 Diabetes

October 16, 2014 | Ferrannini E. | N Engl J Med 2014; 371:1547-1548

CLINICAL PRACTICE

Glycemic Management of Type 2 Diabetes Mellitus

April 5, 2012 | Ismail-Beigi F. | N Engl J Med 2012; 366:1319-1327

Full Text Audio | Comments

PERSPECTIVE

Korea's Thyroid-Cancer "Epidemic" — Screening and Overdiagnosis

November 6, 2014 | Ahn H.S.Kim H.J.Welch H.G. | N Engl J Med 2014; 371:1765-1767

Comments

REVIEW ARTICLE

Ectopic Fat in Insulin Resistance, Dyslipidemia, and Cardiometabolic Disease

September 18, 2014 | Shulman G.I. | N Engl J Med 2014; 371:1131-1141

CLINICAL PRACTICE

Vitamin B_{12} Deficiency

January 10, 2013 | Stabler S.P. | N Engl J Med 2013; 368:149-160

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ORIGINAL ARTICLE

Glycemic Control and Excess Mortality in Type 1 Diabetes

November 20, 2014 | Lind M., Svensson A.-M., Kosiborod M., et al. | N Engl J Med 2014; 371:1972-1982

CME

ORIGINAL ARTICLE

Bariatric Surgery versus Intensive Medical Therapy for Diabetes — 3-Year Outcomes

May 22, 2014 | Schauer P.R., Bhatt D.L., Kirwan J.P., et al. | N Engl J Med 2014; 370:2002-2013

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Glycemic Control and Excess Mortality in Type 1 Diabetes [16,042 views]

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Protecting Progress against Childhood Obesity — The National School Lunch Program [9,067 views]

November 13, 2014 | J.A.W. Baidal and E.M. Taveras

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ORIGINAL ARTICLE

Follow-up of Blood-Pressure Lowering and Glucose Control in Type 2 Diabetes

S. Zoungas, J. Chalmers, B. Neal, L. Billot, Q. Li, Y. Hirakawa, H. Arima, H. Monaghan, R. Joshi, S. Colagiuri, M.E. Cooper, P. Glasziou, D. Grobbee, P. Hamet, S. Harrap, S. Heller, L. Lisheng, G. Mancia, M. Marre, D.R. Matthews, C.E. Mogensen, V. Perkovic, N. Poulter, A. Rodgers, B. Williams, S. MacMahon, A. Patel, and M. Woodward, for the ADVANCE-ON Collaborative Group*

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Zoungas at the George Institute for Global Health, P.O. Box M201, Missenden Rd., Camperdown, NSW 2050, Australia.

Drs. Zoungas and Chalmers, and Drs. Patel and Woodward, contributed equally to this article.

*A complete list of members of the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation Observational Study (ADVANCE-ON) Collaborative Group is provided in the Supplementary Appendix, available at NEJM.org.

This article was published on September 19, 2014, at NEJM.org.

N Engl J Med 2014;371:1392-406.
DOI: 10.1056/NEJMoa1407963

ABSTRACT

BACKGROUND

In the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) factorial trial, the combination of perindopril and indapamide reduced mortality among patients with type 2 diabetes, but intensive glucose control, targeting a glycated hemoglobin level of less than 6.5%, did not. We now report results of the 6-year post-trial follow-up.

METHODS

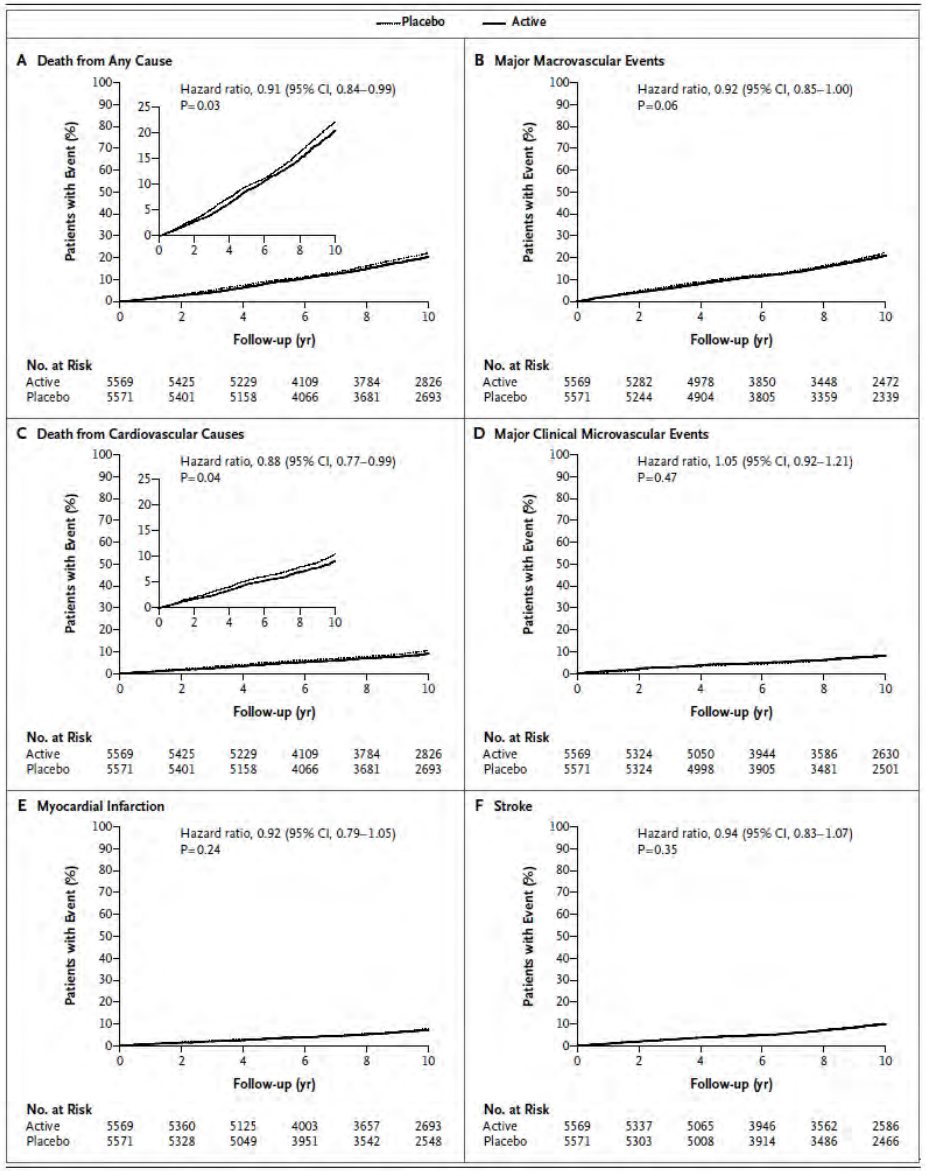
We invited surviving participants, who had previously been assigned to perindopril–indapamide or placebo and to intensive or standard glucose control (with the glucose-control comparison extending for an additional 6 months), to participate in a post-trial follow-up evaluation. The primary end points were death from any cause and major macrovascular events.

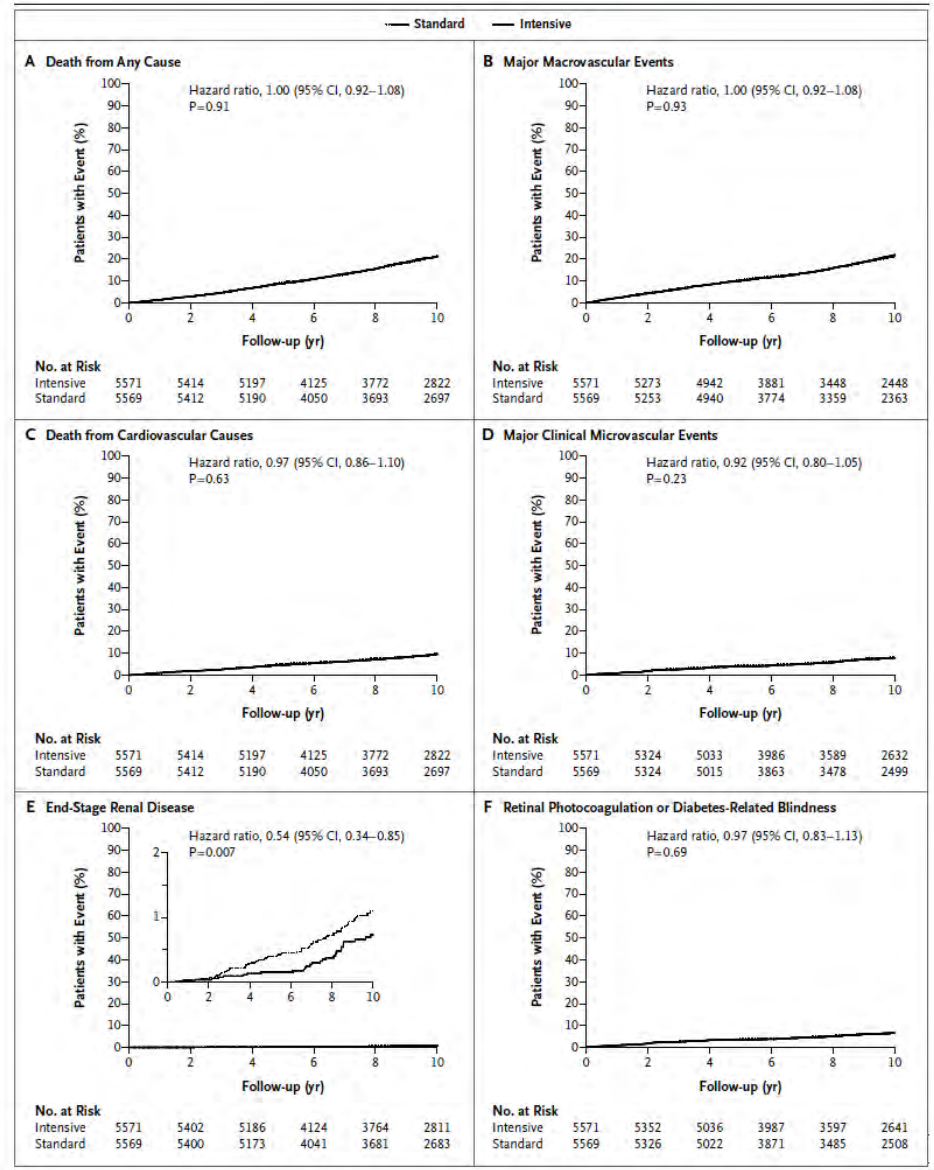
RESULTS

The baseline characteristics were similar among the 11,140 patients who originally underwent randomization and the 8494 patients who participated in the post-trial follow-up for a median of 5.9 years (blood-pressure–lowering comparison) or 5.4 years (glucose-control comparison). Between-group differences in blood pressure and glycated hemoglobin levels during the trial were no longer evident by the first post-trial visit. The reductions in the risk of death from any cause and of death from cardiovascular causes that had been observed in the group receiving active blood-pressure–lowering treatment during the trial were attenuated but significant at the end of the post-trial follow-up; the hazard ratios were 0.91 (95% confidence interval [CI], 0.84 to 0.99; P=0.03) and 0.88 (95% CI, 0.77 to 0.99; P=0.04), respectively. No differences were observed during follow-up in the risk of death from any cause or major macrovascular events between the intensive-glucose-control group and the standard-glucose-control group; the hazard ratios were 1.00 (95% CI, 0.92 to 1.08) and 1.00 (95% CI, 0.92 to 1.08), respectively.

CONCLUSIONS

The benefits with respect to mortality that had been observed among patients originally assigned to blood-pressure–lowering therapy were attenuated but still evident at the end of follow-up. There was no evidence that intensive glucose control during the trial led to long-term benefits with respect to mortality or macrovascular events. (Funded by the National Health and Medical Research Council of Australia and others; ADVANCE-ON ClinicalTrials.gov number, NCT00949286.)





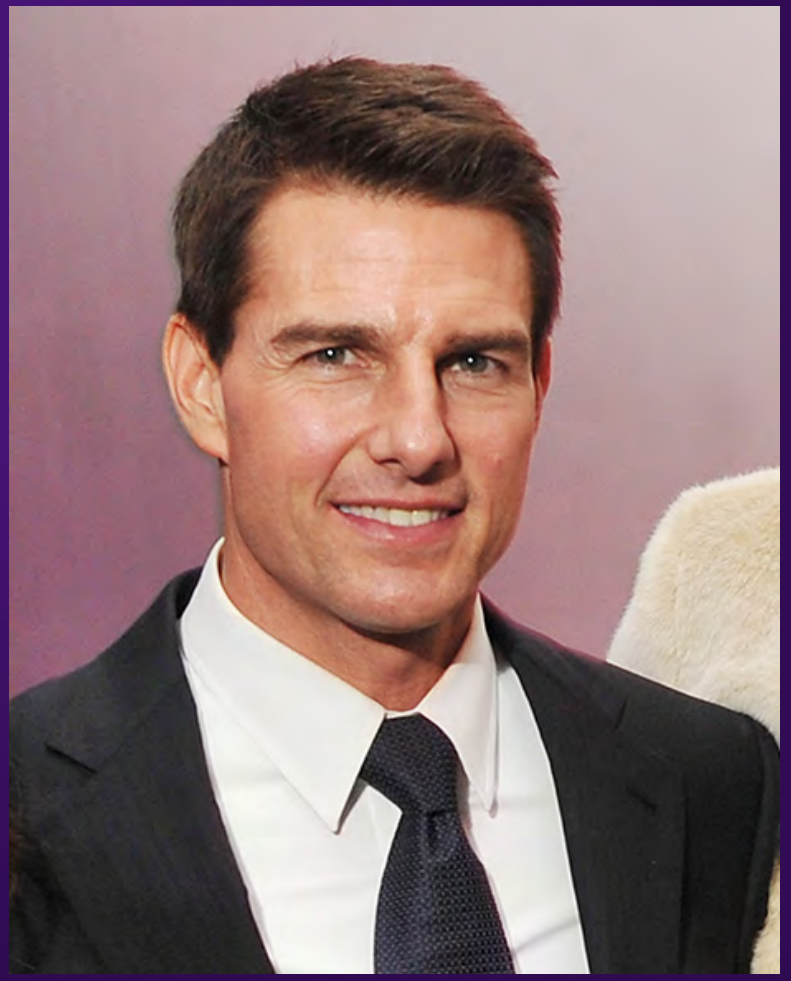
MY Year in Endocrinology: 2014

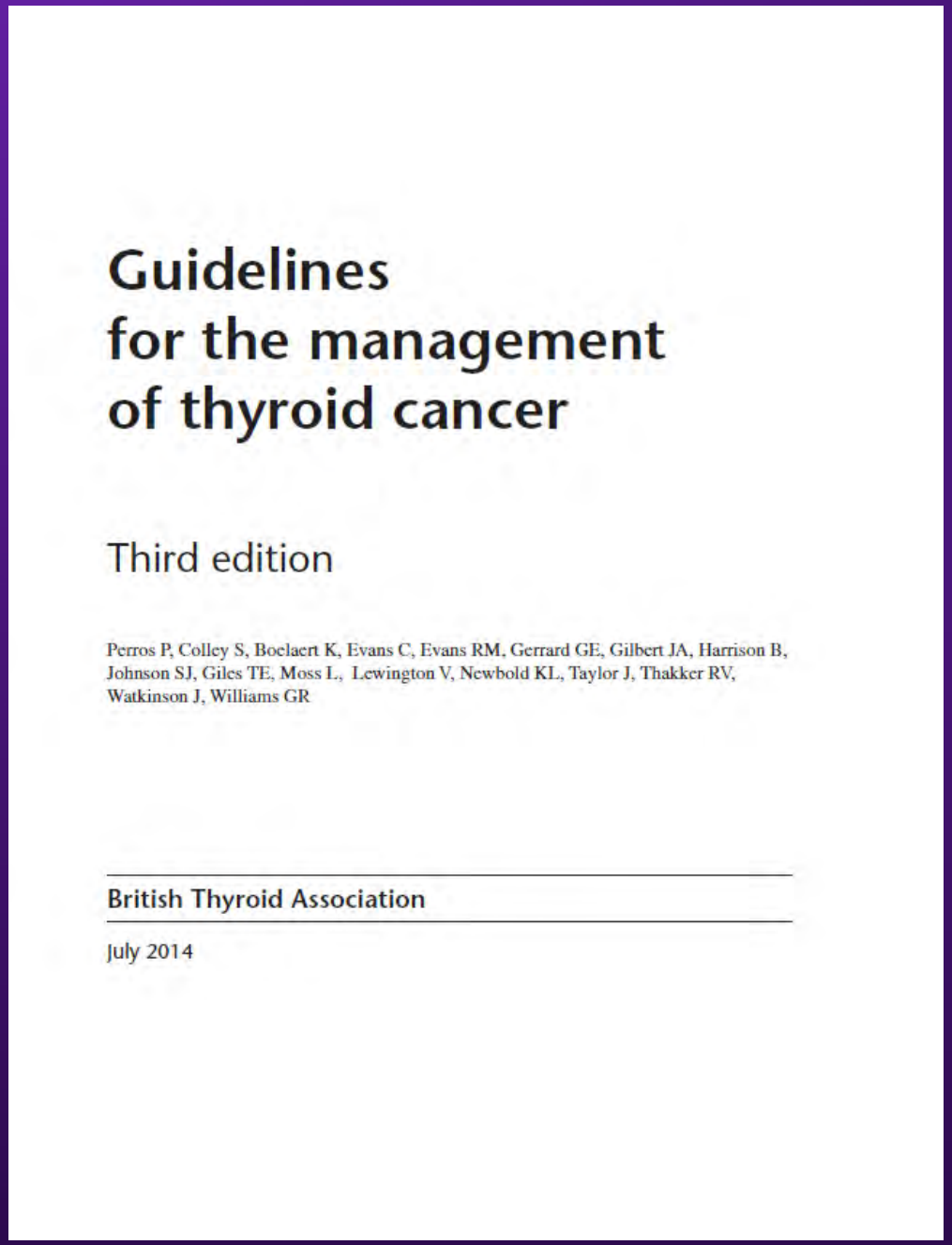
Mark WJ Strachan

Metabolic Unit, Western General Hospital, Edinburgh

Dr Fraser Gibb

Gibb vs Cruise





Impact in SES

- Radiologist has agreed to introduce structured reporting of USS
- Invited other centres contributing to the MDT to do the same
- New referral form for MDT
- Reduced number of patients getting mandatory TSH suppression
- Stopped routine 'therapeutic' radioiodine after lymph node surgery

UCL

NCRI

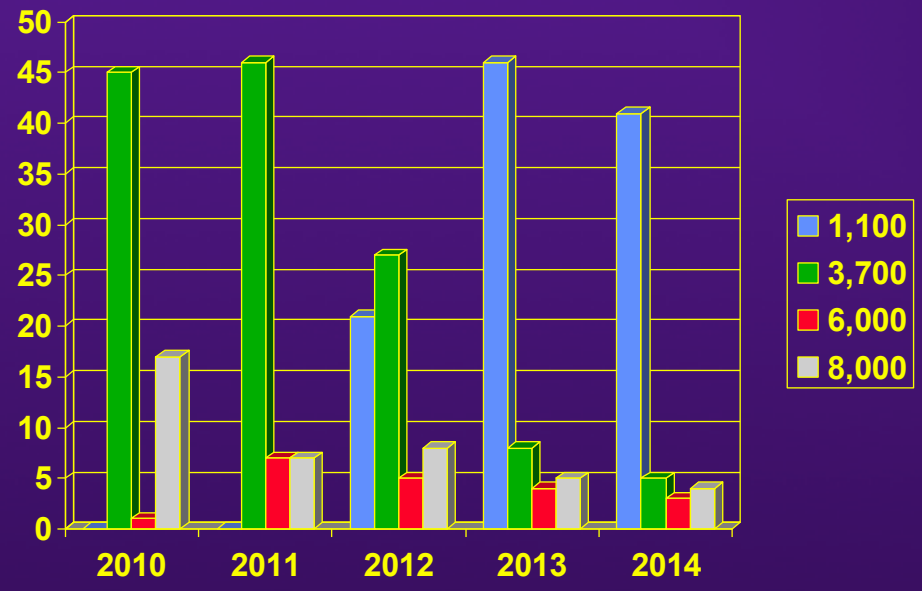
CANCER RESEARCH UK

IoN

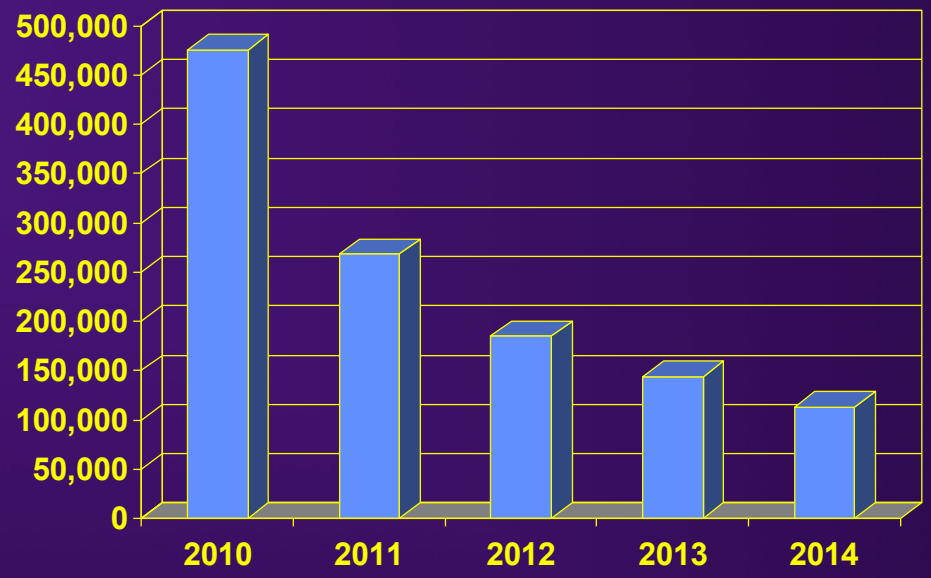
IoN– Is ablative radioiodine Necessary for low risk differentiated thyroid cancer patients

Trial Sponsor:	University College London
Trial Sponsor reference:	UCL/10/0299
Trial funder:	Cancer Research UK
Funder reference:	CRUK/11/010
ISRCTN no:	ISRCTN80416929
Clinical trials.gov no:	NCT01398085
EUDRACT no:	2011-000144-21
CTA no:	23151/0006/001-0001
Protocol version no:	6.1
Protocol version date:	05/07/2013

Radioiodine Prescriptions for Thyroid Cancer at WGH



Individual Prescriptions



Total Activity Prescribed

autumn, a single month providing 5 per cent of the infections. Grassing, paving roads and runways and ultimately the use of highly refined oil on athletic areas were important dust control measures. This control reduced infection rates from one half to two thirds.

2330 Clay Street, San Francisco 15.
2330 Clay Street, San Francisco 15.
636 South Painter Street, Whittier, Calif.
2298 Durant Avenue, Berkeley 4, Calif.

ABSTRACT OF DISCUSSION

DR. RUSSELL V. LEE, San Francisco: Dr. Smith and his associates know more about coccidioidomycosis than any one else, and this work with the Army Air Forces and Ground Forces was a most remarkable piece of combined epidemiology and curative medicine. They surveyed every man in that important military area, important because most of the training fields for the Army Air Forces were located within the area where coccidioidomycosis is prevalent. Dr. Smith was of great help in outlining the problems which might be encountered, and one type threatened to be a considerable menace. It was shown in the paper that dust control could remarkably reduce the incidence of the disease in an area where, left alone, in a year or two the incidence of infection would increase remarkably, and after a number of years' residence in the area we were practically 100 per cent uninfected with coccidioidomycosis. While the mortality was very low, it was the principal cause of hospitalization in many of the Air Force hospitals in that southwest area, so that anything that can be done to reduce it under such circumstances should be done. The incidence under military conditions, particularly under air conditions, was very high. The airplane propeller picks up a lot of dust; soldiers around camps and marching in physical training kick up a lot of dust, and they have become infected at a terrific rate. There was a hospital at San Benito where about one fourth of the men of one detachment were hospitalized and thus saved from going back to this exceedingly dusty region right in the middle of the season of highest incidence. This has lessons for civilian application. This whole desert area has been outlined now largely by the work of Dr. Smith. He can draw a very accurate line around the endemic area of coccidioidomycosis. It is a much larger area than was ever dreamed of before, and when certain types of activities are going to be carried out in that area certain precautions will have to be adopted to protect against coccidioidomycosis. For instance, we had Negro troops in that area, and the Negro is many times more susceptible to coccidioidomycosis than the white man. Negroes should be kept out of that area and the dusty occupations there. It is definitely a hazard for them, judging by the army experience there. In due time there is going to come from Dr. Smith's work the most comprehensive, complete definition of the clinical features as well as the epidemiologic features of coccidioidomycosis. The knowledge of this disease is exactly 50 years old, but in the last five years the whole thing has crystallized. Papers and monographs undoubtedly will appear shortly as a result of this army experience, and this disease is going to be defined with a precision with which it has never been defined before.

Postwar Malaria.—In continental United States civilian malaria in the aggregate is at an all time low; there has been little perceptible change in the past five years. Available data show a marked decrease in malaria rates among continental military personnel since 1941, but in these figures is reflected the extensive control programs in military areas. The cyclic upswing predicted for the early forties by some malariologists has not occurred. In the past two decades reported malaria mortality and morbidity have dropped 85 per cent and 70 per cent respectively.—Hollis, Mark D.: Postwar Malaria Control in Continental United States, *J. Nat. Malaria Soc.*, June 1946.

RADIOACTIVE IODINE THERAPY

Effect on Functioning Metastases of Adenocarcinoma of the Thyroid

S. M. SEIDLIN, M.D.
L. D. MARINELLI, M.A.
and
ELEANOR OSHRY, B.S.
New York

Therapy of neoplastic disease usually consists of two phases: first, the treatment of the primary focus and, second, that of metastases. Specifically, in adenocarcinoma of the thyroid, the primary site together with its immediate extensions is conventionally treated by surgery, radiation or both. Distant metastases, if treated, are usually subjected to palliative external irradiation. This paper is a report of successful therapy of a case of metastatic adenocarcinoma of the thyroid treated by the principle of specific internal irradiation with radioactive iodine.

The earliest study of the uptake of radioactive iodine in 2 cases of carcinoma was reported by Hamilton and his associates [1] in 1940. In 1942 he described 2 more cases [2] in which tracer doses of radioactive iodine had been given to the patients prior to the removal of carcinomatous thyroids. Radioautographs of the excised glands showed no significant deposition of the radioactive iodine in malignant areas in any of these cases.

In April 1942, Keston, Ball, Frantz and Palmer [3] reported the first positive evidence of pickup of the radioactive iodine by a metastasis from a carcinoma of the thyroid. In a patient with multiple lesions, Geiger counter measurements showed appreciable uptake of radioactive iodine in only one of the metastases. Subsequently, from the autopsy, these authors [4] reported that "the bulk of the metastatic tissue was undifferentiated. The metastasis which showed consistent uptake of iodine was the only one which grossly resembled thyroid tissue and which, microscopically, showed chiefly well differentiated tumor."

Leiter, Seidlin, Marinelli and Baumann [5] in a report of 2 cases (1 of which is the subject of the present paper) of hyperthyroidism due to adenocarcinoma of the thyroid and to functioning metastases showed that the effect of thiouracil on the basal metabolic rate, plasma cholesterol, blood iodine and excretion of radioactive iodine in these patients was in every respect

From the Medical Division and Department of Medical Physics of the Montefiore Hospital and the Physics Department of the Memorial Hospital.
A preliminary report of this work was presented at the Clinical Research Meeting of the New York Academy of Medicine on May 16, 1945.
Aided by grants from the Dazian Foundation for Medical Research and from the Lederle Laboratories to Dr. S. M. Seidlin at Montefiore Hospital.
The cooperation of the staffs of the Massachusetts Institute of Technology and Washington University cyclotrons and of Dr. R. D. Evans made this work possible.
Dr. Louis Leiter, Chief of the Medical Division of Montefiore Hospital, gave valuable assistance throughout this work, as did Dr. David Marine and Dr. S. H. Rosen in the field of thyroid pathology and Dr. E. J. Baumann in iodine chemistry. Dr. Solomon Fineman reviewed the roentgenograms. Valuable technical assistance was rendered by Elizabeth F. Focht, Ruth Hill, George Ross, Louella Tulip and Dr. A. A. Yalow.

1. Hamilton, J. G.; Soley, M. H., and Eichorn, K. B.: Deposition of Radioactive Iodine in Human Thyroid Tissue, Univ. California Publ., Pharmacol. **1**: 339-368, 1940.
2. Hamilton, J. G.: The Use of Radioactive Tracers in Biology and Medicine, Radiology **39**: 541-572 (Nov.) 1942.
3. Keston, A. S.; Ball, R. P.; Frantz, V. K., and Palmer, W. W.: Storage of Radioactive Iodine in a Metastasis from Thyroid Carcinoma, Science **95**: 362-363 (April 3) 1942.
4. Frantz, V. K.; Ball, R. P.; Keston, A. S., and Palmer, W. W.: Thyroid Carcinoma with Metastases: Studied with Radioactive Iodine, Ann. Surg. **119**: 668-669 (May) 1944.
5. Leiter, L.; Seidlin, S. M.; Marinelli, L. D., and Baumann, E. J.: Adenocarcinoma of the Thyroid with Hyperthyroidism and Functional Metastases: I. Studies with Thiouracil and Radio-Iodine, J. Clin. Endocrinol. **6**: 247-261 (March) 1946.

Since 1 microcurie of 8 day iodine destroyed per gram of tissue gives approximately 150 equivalent r,[20] to achieve comparable dosage we must concentrate at least 133 microcuries in each cubic centimeter of tumor, if turnover is assumed to be zero. For our patient, with approximately 300 cc. of tumor tissue, such a

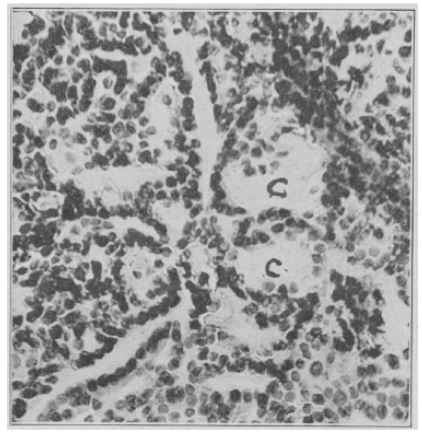


Fig. 9.—Higher magnification (400 times) of section taken at X in figure 7. Note follicular structure and colloid-like material (*c*) in a few follicles.

dose would require that 40 millicures of I^{131} be fixed in the tumors. The actual amount to be fed, however, may be several times this amount, because of the loss of iodine by excretion and by deposition in other tissues, especially if normal thyroid tissue is present.

In addition to these rough quantitative considerations, criteria of a biologic nature, such as the time factor and lack of irradiation of the tumor bed beyond a few millimeters, must be considered in comparing the results of 8 day iodine beta ray therapy with those of 3.82 day radon gamma ray therapy. These remain to be assessed on the basis of additional experience.

Over a period of three years, our patient has received nearly 40,000 equivalent r to each of his tumors. In spite of the remarkable clinical improvement, it cannot be concluded that the functioning tumors have been completely destroyed because recent tracer studies, although showing a marked increase in excretion, still show localization of radioactive iodine in the lesions. Further therapy is indicated and is being planned, the limiting factor being the availability of the isotope in sufficient quantity. The criterion for completion of I * therapy will be the lack of radioactive iodine pickup by any of the known metastases, although the possibility remains that the tumors, even in the absence of any uptake, will not be completely destroyed.

20. A complete description of experimental methods and calculations will be given in a companion paper now in preparation.

All available roentgenograms taken of this patient since July 1939 were reviewed recently in order to evaluate as precisely as possible the progress of the various skeletal lesions. Between July and October of 1939, films were made of the spine, pelvis, skull, arms, legs and left femur. At this time all the regions were negative for metastases. In November 1939, the extraosseous metastatic tumor in the back was removed. By 1941 there were early lesions in the right femur, right ileum and chest as described in the case history. These lesions increased in size, and the one in the skull was discovered in 1943. Frequent plates were taken of all these regions from 1942 until the present, and they show that there was no increase in the area of bone destruction in any region after the first therapeutic dose of I * was administered in 1943. Representative films showing the progress of three of the lesions are shown in figures 10, 11 and 12.

The urinary excretion of radioactive iodine was followed after almost every dose, tracer or therapeutic; on several occasions the collection period was longer than a month. As an illustration, the data obtained after the dose of Aug. 5, 1943, is shown in figure 13. Plotted on semilogarithmic paper, the curve shows two distinct, consecutive rates of change in daily excretion, the break occurring three days after administration. In the same figure a second curve is shown which represents the daily excretion of radioactive iodine by this patient soon after the cessation of thiouracil therapy. The data as a whole seem consistent with the hypothesis that in both instances the excretion of radioactive iodine within three days of administration is governed by a mechanism different from the one which governs its excretion thereafter.

The concentration of radioactive iodine in the blood as a function of time was studied in order to gain information of physiologic and radiologic significance. Shown in figure 14 is a composite curve obtained after

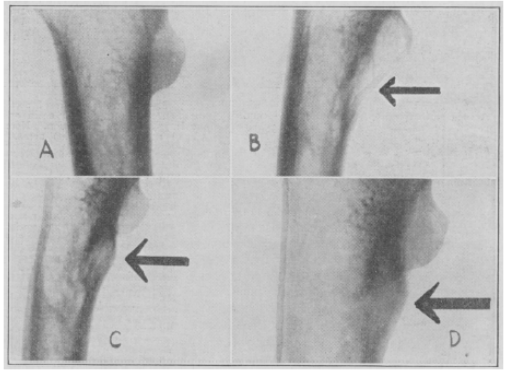


Fig. 10.—Roentgenologic appearance of lesion of the femur on *A*, Oct. 30, 1939; *B*, Oct. 29, 1942; *C*, June 22, 1944; and *D* (a higher magnification), May 22, 1946.

the administration of the last two therapeutic doses of radioactive iodine (April 28, 1944; March 3, 1945). The individual determinations pertaining to each study are shown in detail. The data of Frantz and her associates [4] are also shown for comparison. From the curve it is seen that the level of I * in the blood

DECISION Trial

Sorafenib in radioactive iodine-refractory, locally advanced or metastatic differentiated thyroid cancer: a randomised, double-blind, phase 3 trial

Marcia S Brose, Christopher M Nutting, Barbara Jarzab, Rossella Elisei, Salvatore Siena, Lars Bastholt, Christelle de la Fouchardiere, Furio Pacini, Ralf Paschke, Young Kee Shong, Steven I Sherman, Johannes W A Smit, John Chung, Christian Kappeler, Carol Peña, István Molnár, Martin J Schlumberger, on behalf of the DECISION investigators*

Summary

Background Patients with radioactive iodine (^{131}I)-refractory locally advanced or metastatic differentiated thyroid cancer have a poor prognosis because of the absence of effective treatment options. In this study, we assessed the efficacy and safety of orally administered sorafenib in the treatment of patients with this type of cancer.

Methods In this multicentre, randomised, double-blind, placebo-controlled, phase 3 trial (DECISION), we investigated sorafenib (400 mg orally twice daily) in patients with radioactive iodine-refractory locally advanced or metastatic differentiated thyroid cancer that had progressed within the past 14 months. Adult patients (≥18 years of age) with this type of cancer were enrolled from 77 centres in 18 countries. To be eligible for inclusion, participants had to have at least one measurable lesion by CT or MRI according to Response Evaluation Criteria In Solid Tumors (RECIST); Eastern Cooperative Oncology Group performance status 0–2; adequate bone marrow, liver, and renal function; and serum thyroid-stimulating hormone concentration lower than 0·5 mIU/L. An interactive voice response system was used to randomly allocate participants in a 1:1 ratio to either sorafenib or matching placebo. Patients, investigators, and the study sponsor were masked to treatment assignment. The primary endpoint was progression-free survival, assessed every 8 weeks by central independent review. Analysis was by intention to treat. Patients in the placebo group could cross over to open-label sorafenib upon disease progression. Archival tumour tissue was examined for BRAF and RAS mutations, and serum thyroglobulin was measured at baseline and at each visit. This study is registered with ClinicalTrials.gov, number NCT00984282, and with the EU Clinical Trials Register, number EudraCT 2009–012007–25.

Findings Patients were randomly allocated on a 1:1 basis to sorafenib or placebo. The intention-to-treat population comprised 417 patients (207 in the sorafenib group and 210 in the placebo group) and the safety population was 416 patients (207 in the sorafenib group and 209 in the placebo group). Median progression-free survival was significantly longer in the sorafenib group (10·8 months) than in the placebo group (5·8 months; hazard ratio [HR] 0·59, 95% CI 0·45–0·76; p<0·0001). Progression-free survival improved in all prespecified clinical and genetic biomarker subgroups, irrespective of mutation status. Adverse events occurred in 204 of 207 (98·6%) patients receiving sorafenib during the double-blind period and in 183 of 209 (87·6%) patients receiving placebo. Most adverse events were grade 1 or 2. The most frequent treatment-emergent adverse events in the sorafenib group were hand–foot skin reaction (76·3%), diarrhoea (68·6%), alopecia (67·1%), and rash or desquamation (50·2%).

Interpretation Sorafenib significantly improved progression-free survival compared with placebo in patients with progressive radioactive iodine-refractory differentiated thyroid cancer. Adverse events were consistent with the known safety profile of sorafenib. These results suggest that sorafenib is a new treatment option for patients with progressive radioactive iodine-refractory differentiated thyroid cancer.

Funding Bayer HealthCare Pharmaceuticals and Onyx Pharmaceuticals (an Amgen subsidiary).

Introduction

Differentiated thyroid cancer accounts for about 95% of all thyroid carcinomas worldwide. Differentiated thyroid cancer arises from aberrant follicular cells and is classified histologically as either papillary, follicular (including Hürthle cell), or poorly differentiated.[1,2] Generally, the cancer can be treated effectively with surgery, radioactive iodine, and L-thyroxine therapy.[1,2] However, 7–23% of patients develop distant metastases,[3] two-thirds of whom become refractory to radioactive iodine.[4] These patients have a poor prognosis,[4] and the absence of effective therapy (including chemotherapy) makes their clinical management difficult.[5]

Several genetic alterations have been identified in the molecular pathogenesis of thyroid cancer, most frequently RET–PTC translocations and *BRAF*^{V600E} point mutations in papillary thyroid carcinoma, and *RAS* point mutations in follicular and poorly differentiated thyroid carcinoma.[6] *BRAF*^{V600E} has been associated with poor pathological features and poor clinical outcomes in papillary thyroid carcinoma, although not in all studies.[7–10] Increased expression of vascular endothelial growth

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See Comment page 286

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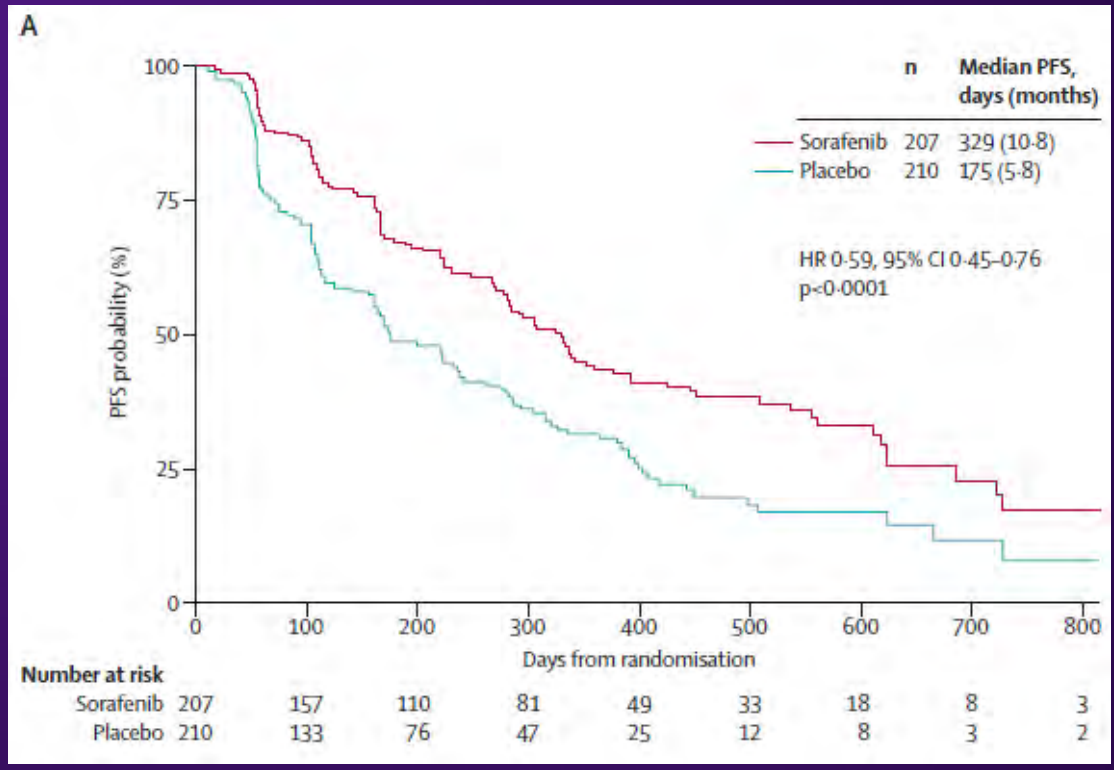

Dr Joyce Baird

1929-2014

Dr Joyce Baird

1929-2014

Clinical practice guideline on diagnosis and treatment of hyponatraemia

Goce Spasovski, Raymond Vanholder[1], Bruno Allolio[2], Djillali Annane[3], Steve Ball[4], Daniel Bichet[5], Guy Decaux[6], Wiebke Fenske[2], Ewout J Hoorn[7], Carole Ichai[8], Michael Joannidis[9], Alain Soupart[6], Robert Zietse[7], Maria Haller[10], Sabine van der Veer[11], Wim Van Biesen[1] and Evi Nagler[1] on behalf of the Hyponatraemia Guideline Development Group

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Abstract

Hyponatraemia, defined as a serum sodium concentration <135 mmol/l, is the most common disorder of body fluid and electrolyte balance encountered in clinical practice. It can lead to a wide spectrum of clinical symptoms, from subtle to severe or even life threatening, and is associated with increased mortality, morbidity and length of hospital stay in patients presenting with a range of conditions. Despite this, the management of patients remains problematic. The prevalence of hyponatraemia in widely different conditions and the fact that hyponatraemia is managed by clinicians with a broad variety of backgrounds have fostered diverse institution- and speciality-based approaches to diagnosis and treatment. To obtain a common and holistic view, the European Society of Intensive Care Medicine (ESICM), the European Society of Endocrinology (ESE) and the European Renal Association – European Dialysis and Transplant Association (ERA–EDTA), represented by European Renal Best Practice (ERBP), have developed the Clinical Practice Guideline on the diagnostic approach and treatment of hyponatraemia as a joint venture of three societies representing specialists with a natural interest in hyponatraemia. In addition to a rigorous approach to methodology and evaluation, we were keen to ensure that the document focused on patient-important outcomes and included utility for clinicians involved in everyday practice.

European Journal of Endocrinology (2014) 170, G1–G47

European Journal of Endocrinology

1. Foreword

Hyponatraemia is a clinical feature in 15–20% of emergency admissions to hospital. It is associated with increased mortality, morbidity and length of hospital stay in patients presenting with a range of conditions. Hyponatraemia is therefore both common and important.

Despite this, the management of patients remains problematic. The prevalence of hyponatraemia under widely different conditions and the fact that hyponatraemia is managed by clinicians with a broad variety of backgrounds have fostered diverse institution- and speciality-based approaches to diagnosis and treatment. However, the paucity of well-designed, prospective studies in the field has limited the evidence-base to these approaches. Previous guidance has often been based on experience or practice, without a systematic approach to evaluation and lacking a clear, patient-centred focus. Clinicians using previous guidance may have noted a number of problems:

- It has been difficult to follow the guidance in day-to-day clinical practice, especially by doctors in training who are managing patients in the 'front line'. Here, the requirement is for clear, concise and practical advice on what has to be done, including during the critical

www.eje-online.org
DOI: 10.1530/EJE-13-1020

Published by Bioscientifica Ltd.
The guidelines were peer reviewed by the owner societies and by external referees prior to publication.

Impact at WGH

- Local Lothian guidelines agreed (renal physicians dragging heels a bit)
- Exponentional rise in in the use of hypertonic saline
- 3% sodium chloride is not available in Scotland – bolusing 300ml 1.8% instead
- 1 bolus is usually sufficient to raise sodium by ~ 5mmol/l
- I am not asking for renin levels as much
- Issue around availability of Demeclocycline – 3 IPTR requests for Tolvaptan

Association of Physicians Meeting, 2014
Homerton College, Cambridge

Evaluation of the Sensitivity and Specificity of ^{11}C-Metomidate Positron Emission Tomography (PET)-CT for Lateralizing Aldosterone Secretion by Conn's Adenomas

Timothy J. Burton, Isla S. Mackenzie, Kottekkattu Balan, Brendan Koo, Nick Bird, Dmitri V. Soloviev, Elena A. B. Azizan, Franklin Aigbirhio, Mark Gurnell, and Morris J. Brown

Clinical Pharmacology Unit (T.J.B., I.S.M., E.A.B.A., M.J.B.), Department of Medicine, University of Cambridge, Cambridge CB2 2QQ, United Kingdom; Department of Radiology (K.B., B.K., N.B.), Addenbrooke's Hospital, Cambridge CB2 2QQ, United Kingdom; and Wolfson Brain Imaging Centre (D.V.S., F.A.) and Institute of Metabolic Science (M.G.), Department of Medicine, University of Cambridge, Cambridge CB2 0QQ, United Kingdom

Context: Identification of unilateral aldosterone-producing (Conn's) adenomas has traditionally required lateralization by the invasive and technically difficult procedure of adrenal vein sampling (AVS). ^{11}C-metomidate, a potent inhibitor of adrenal steroidogenic enzymes, is a positron emission tomography (PET) radiotracer that is selectively accumulated by Conn's adenomas.

Objective: The objective of the study was to compare the sensitivity and specificity of ^{11}C-metomidate PET-computed tomography (CT) against the current gold standard of AVS.

Design: The design of the study was within-patient comparison of diagnostic techniques.

Setting: The study was conducted at a single center-university teaching hospital.

Patients: Thirty-nine patients with primary hyperaldosteronism (PHA) and five with nonfunctioning adenomas (incidentalomas) participated in the study.

Intervention(s): The first six PHA patients were studied on three occasions to determine whether steroid pretreatment reduced ^{11}C-metomidate uptake by normal adrenal. Subsequent patients received dexamethasone for 3 d prior to injection of ^{11}C-metomidate 150–500 MBq.

Main Outcome Measure(s): Maximum standardized uptake values (SUV_{max}) over regions of interest determined from 35–45 min after injection were measured.

Results: Dexamethasone increased tumor to normal adrenal SUV_{max} ratio by 25.6 ± 5.0% ($P < 0.01$). PET-CT visualized subcentimeter adenomas and distinguished hot from cold adenomas within a gland. In 25 patients with PHA and AVS lateralization to the side of an adenoma, SUV_{max} over tumor (mean ± SEM) of 21.7 ± 1.6 was greater than over normal adrenal, 13.8 ± 0.6 ($P = 0.00003$); this difference was absent in 10 patients without lateralization on AVS ($P = 0.28$) and in four of five incidentalomas. On receiver-operator characteristics analysis, an SUV_{max} ratio of 1.25:1 provided a specificity of 87% [95% confidence interval (69, 104)] and sensitivity of 76% (59, 93); in tumors with SUV_{max} greater than 17, the specificity rose to 100%.

Conclusions: ^{11}C-metomidate PET-CT is a sensitive and specific noninvasive alternative to AVS in the management of PHA. (*J Clin Endocrinol Metab* 97: 100–109, 2012)

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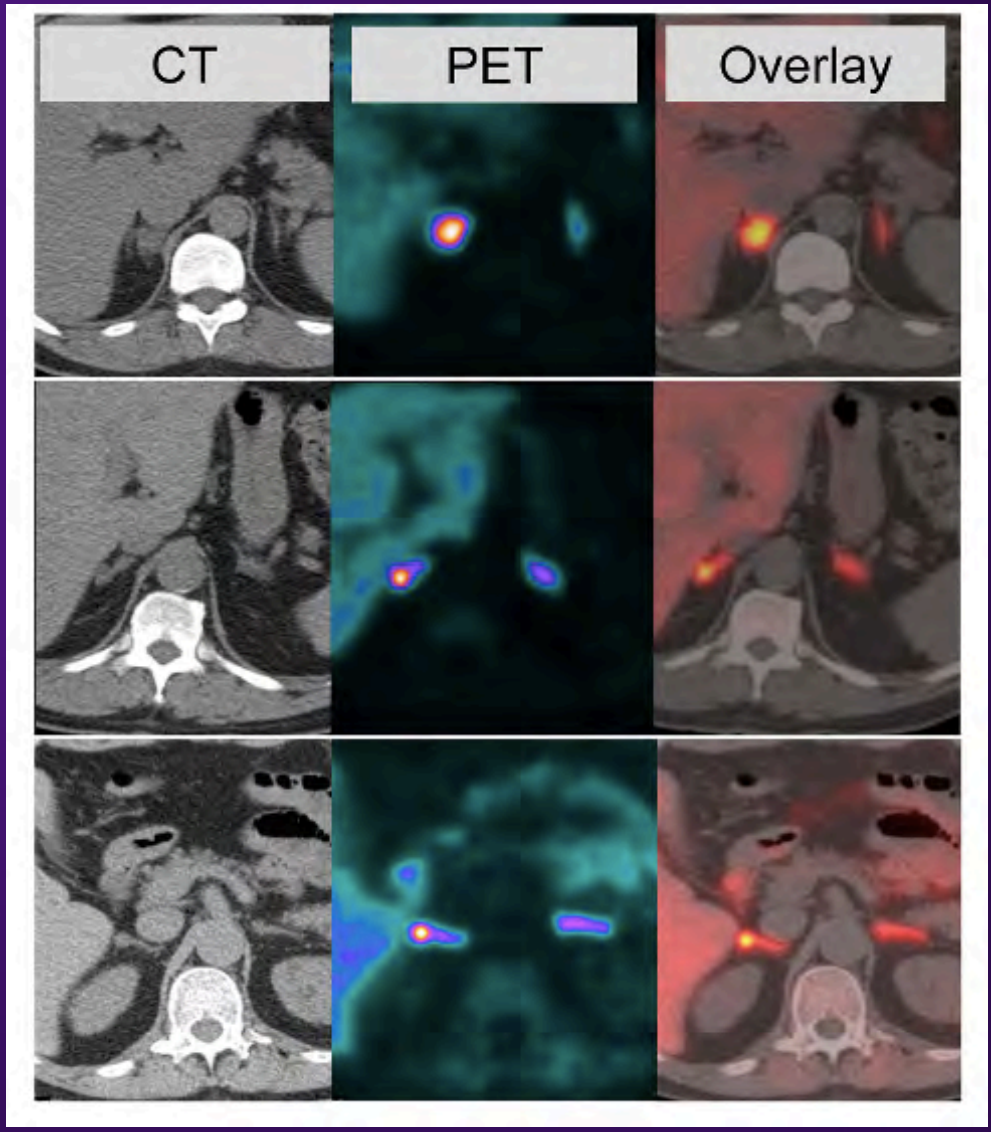
Abbreviations: AVS, Adrenal vein sampling; CI, confidence interval; CT, computed tomography; MRI, magnetic resonance imaging; PET, positron emission tomography; PHA, primary hyperaldosteronism; ROC, receiver-operator characteristic; SUV, standardized uptake values; SUV_{max}, maximum standardized uptake values.



nature genetics

Somatic mutations in *ATP1A1* and *CACNA1D* underlie a common subtype of adrenal hypertension

Elena A B Azizan[1,12], Hanne Poulsen[2,12], Petronel Tuluc[3,12], Junhua Zhou[1,12], Michael V Clausen[2], Andreas Lieb[3], Carmela Maniero[1], Sumedha Garg[4], Elena G Bochukova[4], Wanfeng Zhao[5], Lalarukh Haris Shaikh[1], Cheryl A Brighton[1], Ada E D Teo[1], Anthony P Davenport[1], Tanja Dekkers[6], Bas Tops[7], Benno Küsters[7], Jiri Ceral[8], Giles S H Yeo[4], Sudeshna Guha Neogi[9], Ian McFarlane[9], Nitzan Rosenfeld[10], Francesco Marass[10], James Hadfield[10], Wojciech Margas[11], Kanchan Chaggar[11], Miroslav Solar[8], Jaap Deinum[6], Annette C Dolphin[11], I Sadaf Farooqi[4,12], Joerg Striessnig[3,12], Poul Nissen[2,12] & Morris J Brown[1,12]

At least 5% of individuals with hypertension have adrenal aldosterone-producing adenomas (APAs). Gain-of-function mutations in *KCNJ5* and apparent loss-of-function mutations in *ATP1A1* and *ATP2A3* were reported to occur in APAs[1,2]. We find that *KCNJ5* mutations are common in APAs resembling cortisol-secreting cells of the adrenal zona fasciculata but are absent in a subset of APAs resembling the aldosterone-secreting cells of the adrenal zona glomerulosa[3]. We performed exome sequencing of ten zona glomerulosa–like APAs and identified nine with somatic mutations in either *ATP1A1*, encoding the Na^+/K^+ ATPase α1 subunit, or *CACNA1D*, encoding $Ca_v1.3$. The *ATP1A1* mutations all caused inward leak currents under physiological conditions, and the *CACNA1D* mutations induced a shift of voltage-dependent gating to more negative voltages, suppressed inactivation or increased currents. Many APAs with these mutations were <1 cm in diameter and had been overlooked on conventional adrenal imaging. Recognition of the distinct genotype and phenotype for this subset of APAs could facilitate diagnosis.

APAs are the most common curable cause of hypertension[4,5] and are often due to specific somatic mutations[1,2]. Gain-of-function mutations in the potassium channel *KCNJ5* were found in approximately 40% of APAs[1,3,6,7], and mutations in *ATP1A1* and *ATP2A3*, two P-type ATPases regulating Na^+, K^+ and Ca^{2+} transport, were recently discovered in a further 7% of APAs[2]. Here we report mutations in two genes regulating Na^+, K^+ and Ca^{2+} transport (*ATP1A1* and *CACNA1D*) and highlight the existence of distinct APA subtypes with different mutation profiles. Functional studies of these mutations provide explanations for their dominant effects.

We looked for somatic mutations in APAs with a zona glomerulosa–like phenotype. The zona glomerulosa is the principal site of aldosterone secretion and cell turnover in the adrenal gland, but, paradoxically, classical 'Conn's tumors' tend to resemble cells of the cortisol-secreting

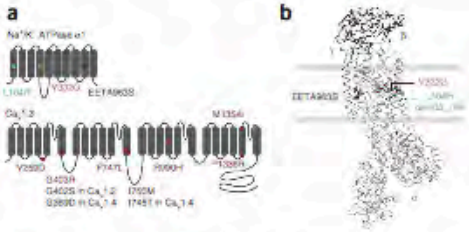


Figure 1 Somatic mutations in *ATP1A1* and *CACNA1D* in APAs. (**a**) Schematic of Na^+/K^+ ATPase subunit α1 and $Ca_v1.3$. Colored circles indicate the positions where somatic alterations or deletions have been described in APAs. (**b**) An overview of the E2.Pi Na^+/K^+ ATPase showing the tripartite complex of α (gray), β (purple) and γ (green) subunits with the extracellular space on top and the membrane represented by two horizontal gray lines. The two occluded K^+ molecules (red) and the substitutions and deletions identified in APAs (colored as in **a**) are indicated. The image was generated with PyMOL using Protein Data Bank (PDB) 2ZXE.

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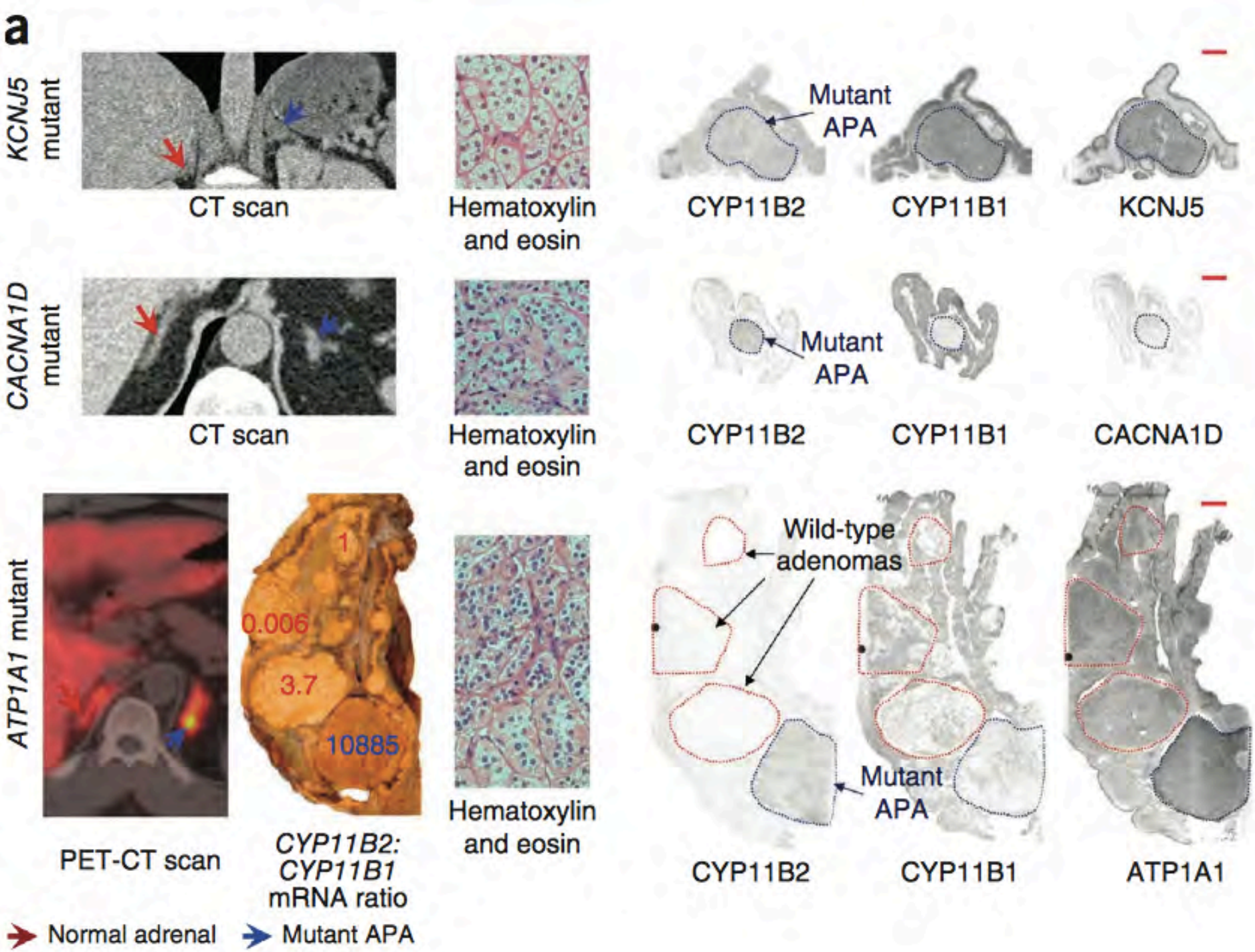
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KCNJ5 mutant
CT scan
Hematoxylin and eosin
Mutant APA
CYP11B2
CYP11B1
KCNJ5
CACNA1D mutant
CT scan
Hematoxylin and eosin
Mutant APA
CYP11B2
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CACNA1D
ATP1A1 mutant
PET-CT scan
1
0.006
3.7
10885
CYP11B2: CYP11B1 mRNA ratio
Hematoxylin and eosin
Wild-type adenomas
Mutant APA
CYP11B2
CYP11B1
ATP1A1
Normal adrenal
Mutant APA


Hillpark Ave
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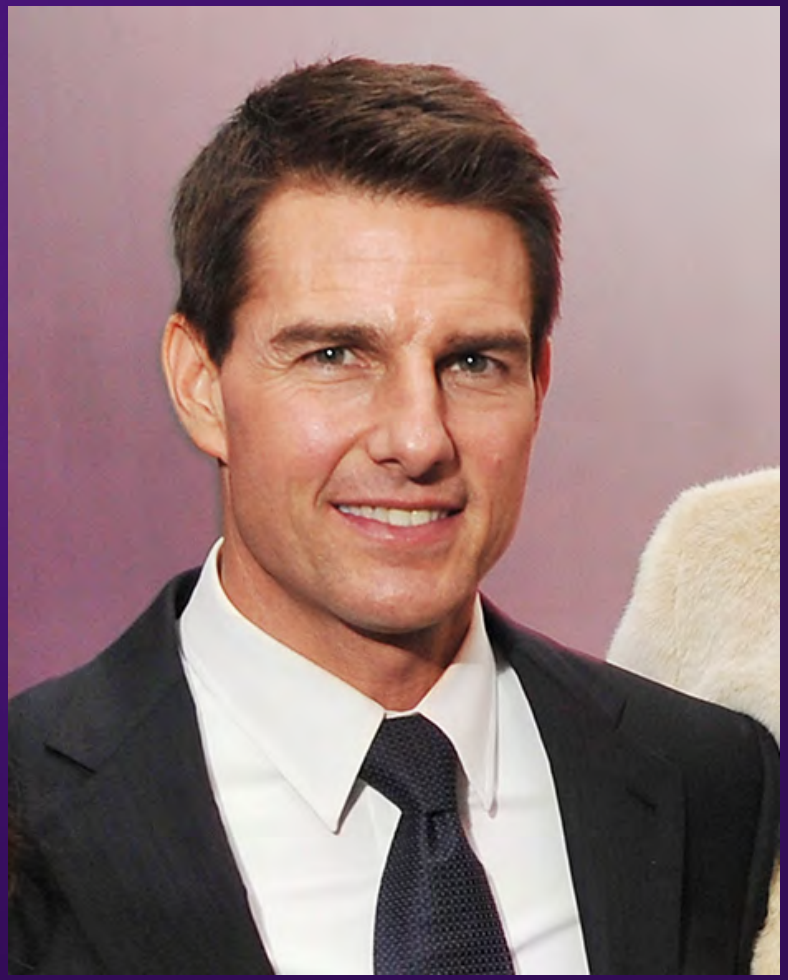

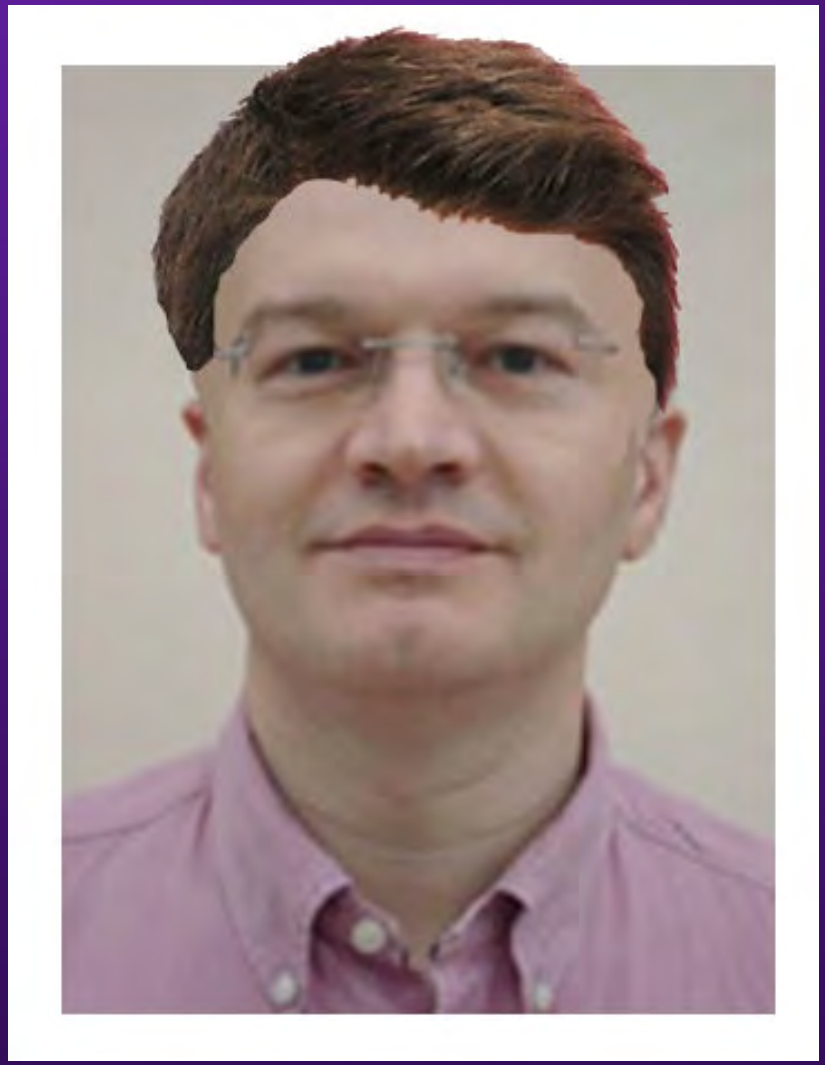

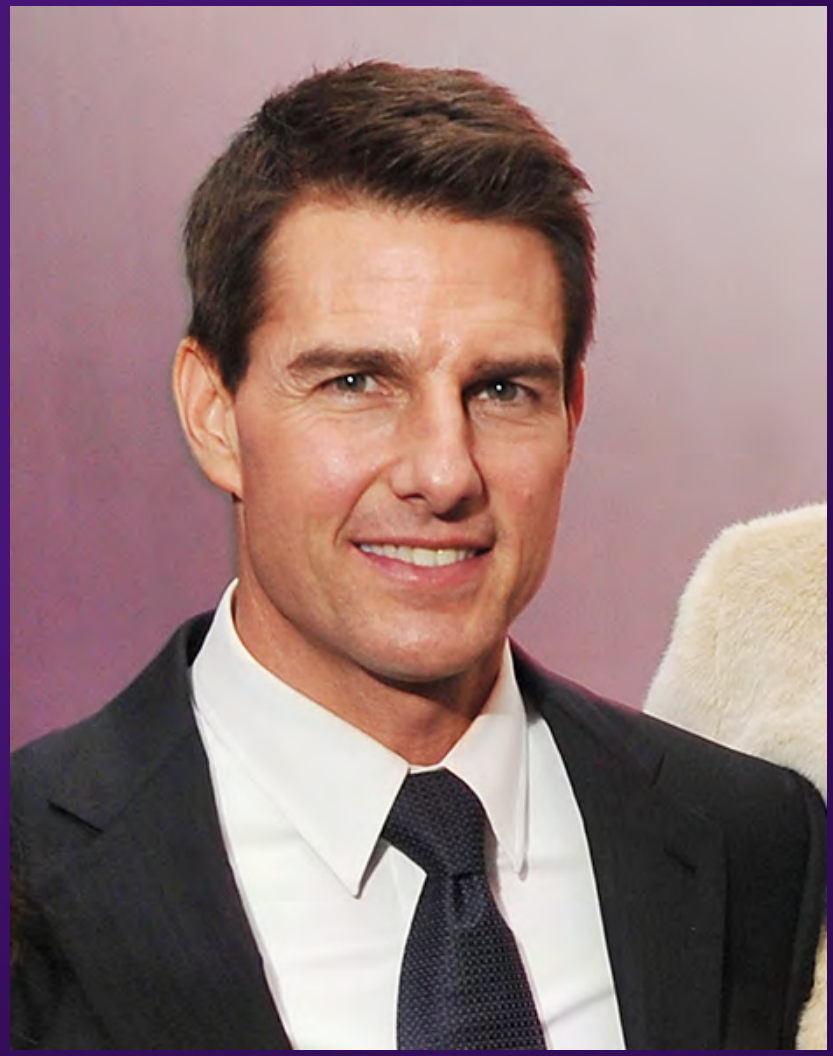

CLARINET Trial

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Lanreotide in Metastatic Enteropancreatic Neuroendocrine Tumors

Martyn E. Caplin, D.M., Marianne Pavel, M.D., Jarosław B. Ćwikła, M.D., Ph.D., Alexandria T. Phan, M.D., Markus Raderer, M.D., Eva Sedláčková, M.D., Guillaume Cadiot, M.D., Ph.D., Edward M. Wolin, M.D., Jaume Capdevila, M.D., Lucy Wall, M.D., Guido Rindi, M.D., Ph.D., Alison Langley, M.Sc., Séverine Martinez, B.Sc., Joëlle Blumberg, M.D., and Philippe Ruszniewski, M.D., Ph.D., for the CLARINET Investigators*

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*Additional investigators in the Controlled Study of Lanreotide Antiproliferative Response in Neuroendocrine Tumors (CLARINET) are listed in the Supplementary Appendix, available at NEJM.org.

N Engl J Med 2014;371:224-33.
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ABSTRACT

BACKGROUND

Somatostatin analogues are commonly used to treat symptoms associated with hormone hypersecretion in neuroendocrine tumors; however, data on their antitumor effects are limited.

METHODS

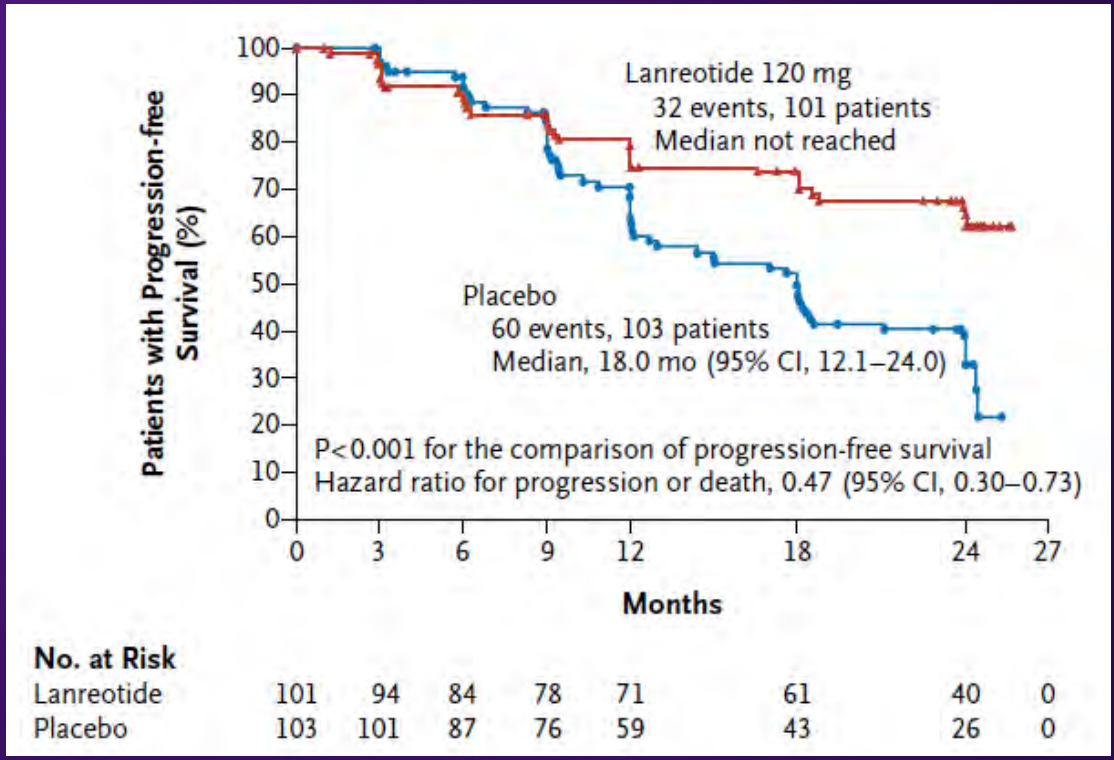
We conducted a randomized, double-blind, placebo-controlled, multinational study of the somatostatin analogue lanreotide in patients with advanced, well-differentiated or moderately differentiated, nonfunctioning, somatostatin receptor–positive neuroendocrine tumors of grade 1 or 2 (a tumor proliferation index [on staining for the Ki-67 antigen] of <10%) and documented disease-progression status. The tumors originated in the pancreas, midgut, or hindgut or were of unknown origin. Patients were randomly assigned to receive an extended-release aqueous-gel formulation of lanreotide (Autogel [known in the United States as Depot], Ipsen) at a dose of 120 mg (101 patients) or placebo (103 patients) once every 28 days for 96 weeks. The primary end point was progression-free survival, defined as the time to disease progression (according to the Response Evaluation Criteria in Solid Tumors, version 1.0) or death. Secondary end points included overall survival, quality of life (assessed with the European Organization for Research and Treatment of Cancer questionnaires QLQ-C30 and QLQ-GLNET21), and safety.

RESULTS

Most patients (96%) had no tumor progression in the 3 to 6 months before randomization, and 33% had hepatic tumor volumes greater than 25%. Lanreotide, as compared with placebo, was associated with significantly prolonged progression-free survival (median not reached vs. median of 18.0 months, P<0.001 by the stratified log-rank test; hazard ratio for progression or death, 0.47; 95% confidence interval [CI], 0.30 to 0.73). The estimated rates of progression-free survival at 24 months were 65.1% (95% CI, 54.0 to 74.1) in the lanreotide group and 33.0% (95% CI, 23.0 to 43.3) in the placebo group. The therapeutic effect in predefined subgroups was generally consistent with that in the overall population, with the exception of small subgroups in which confidence intervals were wide. There were no significant between-group differences in quality of life or overall survival. The most common treatment-related adverse event was diarrhea (in 26% of the patients in the lanreotide group and 9% of those in the placebo group).

CONCLUSIONS

Lanreotide was associated with significantly prolonged progression-free survival among patients with metastatic enteropancreatic neuroendocrine tumors of grade 1 or 2 (Ki-67 <10%). (Funded by Ipsen; CLARINET ClinicalTrials.gov number, NCT00353496; EudraCT 2005-004904-35.)



BRIEF REPORT

Mutant Prolactin Receptor and Familial Hyperprolactinemia

Paul J. Newey, D.Phil., Caroline M. Gorvin, D.Phil., Stephen J. Cleland, Ph.D., Christian B. Willberg, D.Phil., Marcus Bridge, B.Sc., Mohammed Azharuddin, M.B., B.S., Russell S. Drummond, M.D., P. Anton van der Merwe, Ph.D., Paul Klenerman, D.Phil., Chas Bountra, Ph.D., and Rajesh V. Thakker, M.D.

SUMMARY

Hyperprolactinemia that is not associated with gestation or the puerperium is usually due to tumors in the anterior pituitary gland and occurs occasionally in hereditary multiple endocrine neoplasia syndromes. Here, we report data from three sisters with hyperprolactinemia, two of whom presented with oligomenorrhea and one with infertility. These symptoms were not associated with pituitary tumors or multiple endocrine neoplasia but were due to a heterozygous mutation in the prolactin receptor gene, *PRLR*, resulting in an amino acid change from histidine to arginine at codon 188 (His188Arg). This substitution disrupted the high-affinity ligand-binding interface of the prolactin receptor, resulting in a loss of downstream signaling by Janus kinase 2 (JAK2) and signal transducer and activator of transcription 5 (STAT5). Thus, the familial hyperprolactinemia appears to be due to a germline, loss-of-function mutation in *PRLR*, resulting in prolactin insensitivity.

From the Academic Endocrine Unit, Radcliffe Department of Medicine (P.J.N., C.M.G., R.V.T.), Peter Medawar Building for Pathogen Research, Nuffield Department of Medicine (C.B.W., P.K.), Oxford Molecular Pathology Institute, Sir William Dunn School of Pathology (M.B., P.A.M.), and the Structural Genomics Consortium (C.B.), University of Oxford, Oxford, and Glasgow Royal Infirmary, Glasgow (S.J.C., M.A., R.S.D.) — all in the United Kingdom. Address reprint requests to Dr. Thakker at the Radcliffe Department of Medicine, University of Oxford, Oxford Centre for Diabetes, Endocrinology, and Metabolism, Churchill Hospital, Oxford OX3 7LJ, United Kingdom, or at rajesh.thakker@ndm.ox.ac.uk.

Drs. Newey and Gorvin contributed equally to this article.

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PROLACTIN, A HORMONE THAT IS SECRETED PREDOMINANTLY BY LACTOTROPHS in the anterior pituitary gland, is required for the induction and maintenance of lactation in the peripartum and postpartum periods.[1] However, hyperprolactinemia unrelated to pregnancy occurs in approximately 0.1 to 0.3% of the general population[2,3] and may result in infertility, hypogonadism, and galactorrhea. Such nonphysiologic hyperprolactinemia is caused mainly by drugs or by tumors in the anterior pituitary gland, which are usually identifiable by means of magnetic resonance imaging (MRI). Approximately 50% of cases of nonphysiologic hyperprolactinemia are due to prolactinomas[4]; a smaller percentage is due to lesions in the pituitary stalk or systemic disorders (Table S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org).[2,3] However, 10 to 60% of patients with hyperprolactinemia who undergo investigation for a pituitary-based lesion have normal findings on MRI of the pituitary gland,[2,3,5,6] and these patients with idiopathic hyperprolactinemia may have a microadenoma below the limit of MRI detection (<2 mm in diameter) or a different cause of the disorder.[2]

The occurrence of idiopathic hyperprolactinemia in families has suggested a genetic cause, although investigations for mutations of the multiple endocrine neoplasia type 1 gene (*MEN1*), which are associated with prolactinomas, have not detected abnormalities.[7] We hypothesized that familial idiopathic hyperprolactinemia may be due to either abnormalities of the prolactin gene (*PRL*), with the secretion of biologically inactive forms of prolactin, or to prolactin insensitivity

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