

@article{HEERSPINK20191937,

title = "Atrasentan and renal events in patients with type 2 diabetes and chronic kidney disease (SONAR): a double-blind, randomised, placebo-controlled trial",

journal = "The Lancet",

volume = "393",

number = "10184",

pages = "1937 - 1947",

year = "2019",

issn = "0140-6736",

doi = "https://doi.org/10.1016/S0140-6736(19)30772-X",

url = "http://www.sciencedirect.com/science/article/pii/S014067361930772X",

author = "Hiddo J L Heerspink and Hans-Henrik Parving and Dennis L Andress and George Bakris and Ricardo Correa-Rotter and Fan-Fan Hou and Dalane W Kitzman and Donald Kohan and Hirofumi Makino and John J V McMurray and Joel Z Melnick and Michael G Miller and Pablo E Pergola and Vlado Perkovic and Sheldon Tobe and Tingting Yi and Melissa Wigderson and Dick {de Zeeuw} and Alicia Elbert and Augusto Vallejos and Andres Alvarisqueta and Laura Maffei and Luis Juncos and Javier {de Arteaga} and Gustavo Greloni and Eduardo Farias and Alfredo Zucchini and Daniel Vogel and Ana Cusumano and Juan Santos and Margaret Fraenkel and Martin Gallagher and Tim Davis and Shamasunder Acharya and Duncan Cooke and Michael Suranyi and Simon Roger and Nigel Toussaint and Carol Pollock and Doris Chan and Stephen Stranks and Richard Maclsaac and Zoltan Endre and Alice Schmidt and Rudolf Prager and Gert Mayer and Xavier Warling and Michel Jadoul and Jean Hougardy and Chris Verammen and Bruno {Van Vlem} and Pieter Gillard and Adriana {Costa e Forti} and Joao Lindolfo Borges and Luis {Santos Canani} and Freddy Eliaschewitz and Silmara Leite and Fadlo {Fraige Filho} and Raphael Paschoalin and Jose Andrade {Moura Neto} and Luciane Deboni and Irene {de Lourdes Noronha} and Cintia Cercato and Carlos Alberto Prompt and Maria Zanella and Nelson Rassi and Domingos D'Avila and Rosangela Milagres and Joao Felicio and Roberto {Pecoits Filho} and Miguel Carlos Riella and Joao Salles and Elizete Keitel and Sergio Draibe and Celso Amodeo and Joseph Youmbissi and Louise Roy and Serge Cournoyer and Shivinder Jolly and Vincent Pichette and Gihad Nesrallah and Harpreet Singh Bajaj and Hasnain Khandwala and Ronnie Aronson and Richard Goluch and Paul Tam and Christian Rabbat and Sheldon Tobe and Gordon Bailey and Stephen Chow and Alvaro Castillo and Alfredo {Danin Vargas} and Fernando Gonzalez and Rodrigo Munoz and Vicente Gutierrez and Gonzalo Godoy and Hongwen Zhao and Zhangsuo Liu and Minghui Zhao and Xiaohui Guo and Benli Su and Shuxia Fu and Yan Xu and Jinkui Yang and Bingyin Shi and Guanqing Xiao and Wei Shi and Chuanming Hao and Changying Xing and Fanfan Hou and Qun Luo and Yuxiu Li and Linong Ji and Li Zuo and Song Wang and Zhaohui Ni and Guohua Ding and Nan Chen and Jiajun Zhao and Weiping Jia and Shengqiang Yu and Jian Weng and Gang Xu and Ping Fu and Shiren Sun and Bicheng Liu and Xiaoqiang Ding and Ivan Rychlik and Alexandra Oplustilova and Dagmar Bartaskova and Vaclava Honova and Hana Chmelickova and Martin Petr and Petr Bucek and Vladimir Tesar and Emil Zahumensky and Johan Povlsen and Kenneth Egstrup and Anna Oczachowska-Kulik and Peter Rossing and Jorma Lahtela and Jorma Strand and Ilkka Kantola and Catherine Petit and Christian Combe and Philippe Zaoui and Vincent Esnault and Pablo {Urena Torres}

and Jean-Michel Halimi and Bertrand Dussol and Tasso Bieler and Klemens Budde and Frank Dellanna and Thomas Segiet and Christine Kosch and Hans Schmidt-Guertler and Isabelle Schenkenberger and Volker Vielhauer and Frank Pistrosch and Mark Alscher and Christoph Hasslacher and Christian Hugo and Anja Muehlfeld and Christoph Wanner and Ploumis Passadakis and Theofanis Apostolou and Nikolaos Tentolouris and Ioannis Stefanidis and Konstantinos Mavromatidis and Vasilios Liakopoulos and Dimitrios Goumenos and Konstantinos Siamopoulos and Vincent Yeung and Risa Ozaki and Samuel Fung and Kathryn Tan and Sydney Tang and Sing Leung Lui and Siu Fai Cheung and Seamus Sreenan and Joseph Eustace and Donal O'Shea and Peter Lavin and Austin Stack and Yoram Yagil and Julio Wainstein and Hilla Knobler and Josef Cohen and Irina Kenis and Deeb Daoud and Yosefa Bar-Dayana and Victor Frajewicki and Faiad Adawi and Loreto Gesualdo and Domenico Santoro and Francesco Marino and Andrea Galfre and Chiara Brunati and Piero Ruggenenti and Giuseppe Rombola and Giuseppe Pugliese and Maura Ravera and Fabio Malberti and Giuseppe Pontoriero and Teresa Rampino and Salvatore {De Cosmo} and Ciro Esposito and Felice Nappi and Cataldo Abaterusso and Giuseppe Conte and Vincenzo Panichi and Davide Lauro and Giovambattista Capasso and Domenico Russo and Jiichi Anzai and Motoji Naka and Keita Ato and Tetsuro Tsujimoto and Toshinori Nimura and Eitaro Nakashima and Tetsuro Takeda and Shinya Fujii and Kunihisa Kobayashi and Hideaki Iwaoka and Koji Nagayama and Hiroyuki Harada and Hajime Maeda and Rui Kishimoto and Tadashi Iitsuka and Naoki Itabashi and Ryuichi Furuya and Yoshitaka Maeda and Daishiro Yamada and Nobuhiro Sasaki and Hiromitsu Sasaki and Shinichiro Ueda and Naoki Kashihara and Shuichi Watanabe and Takehiro Nakamura and Hidetoshi Kanai and Yuichiro Makita and Keiko Ono and Noriyuki Iehara and Daisuke Goto and Keiichiro Kosuge and Kenichi Tsuchida and Toshiaki Sato and Takashi Sekikawa and Hideki Okamoto and Tsuyoshi Tanaka and Naoko Ikeda and Takenobu Tadika and Koji Mukasa and Takeshi Osonoi and Fuminori Hirano and Motonobu Nishimura and Yuko Yambe and Yukio Tanaka and Makoto Ujihara and Takashi Sakai and Mitsuo Imura and Yutaka Umayahara and Shinya Makino and Jun Nakazawa and Yukinari Yamaguchi and Susumu Kashine and Hiroaki Miyaoka and Katsunori Suzuki and Toshihiko Inoue and Sou Nagai and Nobuyuki Sato and Masahiro Yamamoto and Noriyasu Taya and Akira Fujita and Akira Matsutani and Yugo Shibagaki and Yuichi Sato and Akira Yamauchi and Masahiro Tsutsui and Tamayo Ishiko and Shizuka Kaneko and Nobuyuki Azuma and Hirofumi Matsuda and Yasuhiro Hashiguchi and Yukiko Onishi and Mikiya Tokui and Munehide Matsuhisa and Arihiro Kiyosue and Junji Shinoda and Kazuo Ishikawa and Ghazali Ahmad and Shalini Vijayasingham and Nor Azizah Aziz and Zanariah Hussein and Yin Khet Fung and Wan Hasnul Halimi Wan Hassan and Hin Seng Wong and Bak Leong Goh and Norhaliza Mohd Ali and Nor Shaffinaz Yusuf Azmi Merican and Indralingam Vaithilingam and Nik Nur Fatnoon {Nik Ahmad} and Noor Adam and Norlela Sukor and V Paranthaman P Vengadasalam and Khalid {Abdul Kadir} and Mafauzy Mohamed and Karina {Renoirte Lopez} and Aniceto Leguizamo-Dimas and Alfredo {Chew Wong} and Jose Chevaile-Ramos and Jose {Gonzalez Gonzalez} and Raul {Rico Hernandez} and Jose Nino-Cruz and Leobardo {Sauque Reyna} and Guillermo Gonzalez-Galvez and Magdalena {Madero Rovalo} and Tomasso Bochicchio-Ricardelli and Jorge Aldrete and Jaime Carranza-Madrigal and Liffert Vogt and Peter {Smak Gregoor} and JNM Barendregt and Peter Luik and Ronald Gansevoort and Gozewijn Laverman and Helen Pilmore and Helen Lunt and John Baker and Steven Miller and Kannaiyan Rabindranath and Luis Zapata-Rincon and Rolando Vargas-Gonzales and Jorge {Calderon Ticona} and Augusto {Dextre Espinoza} and Jose {Burga Nunez} and Carlos Antonio Zea-Nunez and Benjamin {Herrada Orue} and Boris Medina-Santander and Cesar Delgado-Butron and Julio Farfan-Aspilcueta and Stanislaw Mazur and Miroslaw Necki and Michal Wruk and Katarzyna Klodawska and Grazyna Popena and Ewa Skokowska and Malgorzata Arciszewska and Andrzej Wiecek and Kazimierz Ciechanowski and Michal Nowicki and Rita Birne and Antonio Cabrita and Aura Ramos and Manuel Anibal {Antunes Ferreira} and Evelyn {Matta Fontanet} and Altagracia Aurora Alcantara-Gonzalez and Angel Comulada-Rivera and Eugenia {Galindo Ramos} and Jose Cangiano and Luis Quesada-Suarez and Ricardo {Calderon Ortiz} and Jose Vazquez-

Tanus and Rafael Burgos-Calderon and Carlos Rosado and Nicolae Hancu and Ella Pintilei and Cristina Mistodie and Gabriel Bako and Lavinia Ionutiu and Ligia Petrica and Romulus Timar and Liliana Tuta and Livia Duma and Adriana Tutescu and Svetlana Ivanova and Ashot Essaian and Konstantin Zrazhevskiy and Natalia Tomilina and Elena Smolyarchuk and Anatoly Kuzin and Olga Lantseva and Irina Karpova and Minara Shamkhalova and Natalia Liberanskaya and Andrey Yavdosyuk and Yuri Shvarts and Tatiana Bardymova and Olga Blagoveshchenskaya and Oleg Solovev and Elena Rechkova and Natalia Pikalova and Maria Pavlova and Elena Kolmakova and Rustam Sayfutdinov and Svetlana Villevalde and Natalya Koziolova and Vladimir Martynenko and Vyacheslav Marasaev and Adelya Maksudova and Olga Sigitova and Viktor Mordovin and Vadim Klimontov and Yulia Samoylova and Tatiana Karonova and Lee Ying Yeoh and Boon Wee Teo and Marjorie Wai Yin Foo and Adrian Liew and Ivan Tkac and Aniko Oroszova and Jozef Fekete and Jaroslav Rosenberger and Ida Obetkova and Alla Fulopova and Eva Kolesarova and Katarina Raslova and Peter Smolko and Adrian Oksa and Larry Distiller and Julien Trokis and Luthando Adams and Hemant Makan and Padaruth Ramlachan and Essack Mitha and Kathleen Coetzee and Zelda Punt and Qasim Bhorat and Puvenesvari Naiker and Graham Ellis and Louis {Van Zyl} and Kwan Woo Lee and Min Seon Kim and Soon-Jib Yoo and Kun Ho Yoon and Yong-Wook Cho and Tae-Sun Park and Sang Yong Kim and Moon-Gi Choi and Tae Keun Oh and Kang-Wook Lee and Ho Sang Shon and Sung Hwan Suh and Byung-Joon Kim and Kim Doo-Man and Joo Hark Yi and Sang Ah Lee and Ho Chan Cho and Sin-Gon Kim and Dae-Ryong Cha and Ji A Seo and Kyung Mook Choi and Jeong-Taek Woo and Kyu Jeung Ahn and Jae Hyuk Lee and In-Joo Kim and Moon-Kyu Lee and Hak Chul Jang and Kyong-Soo Park and Beom Seok Kim and Ji Oh Mok and Mijung Shin and Sun Ae Yoon and Il-Seong Nam-Goong and Choon Hee Chung and Tae Yang Yu and Hyoung Woo Lee and Alfonso {Soto Gonzalez} and Jaime Almirall and Jesus Egido and Francesca {Calero Gonzalez} and Gema {Fernandez Fresnedo} and Ildefonso {Valera Cortes} and Manuel {Praga Terente} and Isabel {Garcia Mendez} and Juan {Navarro Gonzalez} and Jose {Herrero Calvo} and Secundino {Cigarran Guldris} and Mario {Prieto Velasco} and Jose Ignacio {Minguela Pesquera} and Antonio Galan and Julio Pascual and Maria {Marques Vidas} and Judith {Martins Munoz} and Jose Rodriguez-Perez and Cristina Castro-Alonso and Josep {Bonet Sol} and Daniel Seron and Elvira {Fernandez Giraldez} and Javier {Arrieta Lezama} and Nuria Montero and Julio Hernandez-Jaras and Rafael {Santamaria Olmo} and Jose Ramon {Molas Coten} and Olof Hellberg and Bengt Fellstrom and Andreas Bock and Dee Pei and Ching-Ling Lin and Kai-Jen Tien and Ching-Chu Chen and Chien-Ning Huang and Ju-Ying Jiang and Du-An Wu and Chih-Hsun Chu and Shih-Ting Tseng and Jung-Fu Chen and Cho-Tsan Bau and Wayne Sheu and Mai-Szu Wu and Ramazan Sari and Siren Sezer and Alaattin Yildiz and Ilhan Satman and Betul Kalender and Borys Mankovskyy and Ivan Fushtey and Mykola Stanislavchuk and Mykola Kolenyk and Iryna Dudar and Viktoriia Zolotaikina and Orest Abrahamovych and Tetyana Kostynenko and Olena Petrosyan and Petro Kuskalo and Olga Galushchak and Oleg Legun and Ivan Topchii and Liliya Martynyuk and Vasyl Stryzhak and Svitlana Panina and Sergii Tkach and Vadym Korpachev and Peter Maxwell and Luigi Gnudi and Sui Phin Kon and Hilary Tindall and Phillip Kalra and Patrick Mark and Dipesh Patel and Mohamed El-Shahawy and Liqun Bai and Romanita Nica and Yeong-Hau Lien and Judson Menefee and Robert Busch and Alan Miller and Azazuddin Ahmed and Ahmed Arif and Joseph Lee and Sachin Desai and Shweta Bansal and Marie Bentsianov and Mario Belledonne and Charles Jere and Raul Gaona and Gregory Greenwood and Osvaldo Brusco and Mark Boiskin and Diogo Belo and Raffi Minasian and Naveen Atray and Mary Lawrence and John Taliercio and Pablo Pergola and David Scott and German Alvarez and Bradley Marder and Thomas Powell and Wa'el Bakdash and George Stoica and Christopher McFadden and Marc Rendell and Jonathan Wise and Audrey Jones and Michael Jardula and Ivy-Joan Madu and Freemu Varghese and Brian Tulloch and Ziauddin Ahmed and Melanie Hames and Imran Nazeer and Newman Shahid and Rekha John and Manuel Montero and David Fitz-Patrick and Lawrence Phillips and Antonio Guasch and Elena Christofides and Aijaz Gundroo and Mohammad Amin and Cynthia Bowman-Stroud and Michael Link and Laura Mulloy and Michael

Nammour and Tarik Lalwani and Lenita Hanson and Adam Whaley-Connell and Lee Herman and Rupi Chatha and Sayed Osama and Kenneth Liss and Zeid Kayali and Anuj Bhargava and Ezra Israel and Alfredo Peguero-Rivera and Michael Fang and Judith Slover and Elena Barendolts and Jose Flores and Rosemary Muoneke and Virginia Savin and Stella Awua-Larbi and Andrew Levine and George Newman and Laden Golestaneh and Guillermo Bohm and Efrain Reisin and Lucita Cruz and Robert Weiss and Franklin Zieve and Edward Horwitz and Peale Chuang and James Mersey and John Manley and Ronald Graf and Fadi Bedros and Sudhir Joshi and Juan Frias and Ali Assefi and Andrew O'Shaughnessy and Roman Brantley and Todd Minga and David Tietjen and Samuel Kantor and Aamir Jamal and Ramon Guadiz and Kenneth Hershon and Peter Bressler and Nelson Kopyt and Harold Cathcart and Scott Bloom and Ronald Reichel and Samer Nakhle and Emily Dulude and Joshua Tarkan and Penelope Baker and Steven Zeig and Jaynier {Moya Hechevarria} and Armando Roperro-Cartier and Gilda {De la Calle} and Ankur Doshi and Fadi Saba and Teresa Sligh and Sylvia Shaw and Jayant Kumar and Harold Szerlip and George Bayliss and Alan Perlman and Lakhi Sakhrani and Steven Gouge and Georges Argoud and Idalia Acosta and John Elder and Sucharit Joshi and John Sensenbrenner and Steven Vicks and Roberto Mangoo-Karim and Claude Galphin and Carlos Leon-Forero and John Gilbert and Eric Brown and Adeel Ijaz and Salman Butt and Mariana Markell and Carlos Arauz-Pacheco and Lance Sloan and Odilon Alvarado and Serge Jabbour and Eric Simon and Anjay Rastogi and Sam James and George Bakris and Karen Hall and John Melish and Brad Dixon and Allen Adolphe and Csaba Kovesdy and Srinivasan Beddhu and Richard Solomon and Ronald Fernando and Ellis Levin and Charuhas Thakar and Brooks Robey and David Goldfarb and Linda Fried and Geetha Maddukuri and Stephen Thomson and Andrew Annand and Saeed Kronfli and Paramjit Kalirao and Rebecca Schmidt and Neera Dahl and Samuel Blumenthal and Debra Weinstein and Ove Ostergaard and Talia Weinstein and Yasuhiro Ono and Murat Yalcin and Shahana Karim",

abstract = "Summary

## Background

Short-term treatment for people with type 2 diabetes using a low dose of the selective endothelin A receptor antagonist atrasentan reduces albuminuria without causing significant sodium retention. We report the long-term effects of treatment with atrasentan on major renal outcomes.

## Methods

We did this double-blind, randomised, placebo-controlled trial at 689 sites in 41 countries. We enrolled adults aged 18–85 years with type 2 diabetes, estimated glomerular filtration rate (eGFR) 25–75 mL/min per 1.73 m<sup>2</sup> of body surface area, and a urine albumin-to-creatinine ratio (UACR) of 300–5000 mg/g who had received maximum labelled or tolerated renin–angiotensin system inhibition for at least 4 weeks. Participants were given atrasentan 0.75 mg orally daily during an enrichment period before random group assignment. Those with a UACR decrease of at least 30% with no substantial fluid retention during the enrichment period (responders) were included in the double-blind treatment period. Responders were randomly assigned to receive either atrasentan 0.75 mg orally daily or placebo. All patients and investigators were masked to treatment assignment. The primary endpoint was a composite of doubling of serum creatinine (sustained for ≥30 days) or end-stage kidney disease (eGFR <15 mL/min per 1.73 m<sup>2</sup> sustained for ≥90 days, chronic dialysis for ≥90 days, kidney transplantation, or death from kidney failure) in the intention-to-treat population of all responders. Safety was assessed in all patients who received at least one dose of their assigned study treatment. The study is registered with ClinicalTrials.gov, number NCT01858532.

## Findings

Between May 17, 2013, and July 13, 2017, 11 087 patients were screened; 5117 entered the enrichment period, and 4711 completed the enrichment period. Of these, 2648 patients were responders and were randomly assigned to the atrasentan group (n=1325) or placebo group (n=1323). Median follow-up was 2.2 years (IQR 1.4–2.9). 79 (6.0%) of 1325 patients in the atrasentan group and 105 (7.9%) of 1323 in the placebo group had a primary composite renal endpoint event (hazard ratio [HR] 0.65 [95% CI 0.49–0.88]; p=0.0047). Fluid retention and anaemia adverse events, which have been previously attributed to endothelin receptor antagonists, were more frequent in the atrasentan group than in the placebo group. Hospital admission for heart failure occurred in 47 (3.5%) of 1325 patients in the atrasentan group and 34 (2.6%) of 1323 patients in the placebo group (HR 1.33 [95% CI 0.85–2.07]; p=0.208). 58 (4.4%) patients in the atrasentan group and 52 (3.9%) in the placebo group died (HR 1.09 [95% CI 0.75–1.59]; p=0.65).

## Interpretation

Atrasentan reduced the risk of renal events in patients with diabetes and chronic kidney disease who were selected to optimise efficacy and safety. These data support a potential role for selective endothelin receptor antagonists in protecting renal function in patients with type 2 diabetes at high risk of developing end-stage kidney disease.

## Funding

AbbVie."

}