Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

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Supplementary Appendix

CANVAS and CANVAS-R sites and investigators

CANVAS

Argentina: Pablo Arias, Maria Rosa Ulla, Andres Alvarisqueta, Laura Maffei, Jose Osvaldo Fretes, Silvia Gorban De Lapertosa, Virginia Visco, Georgina Sposetti, Javier Farias, Eduardo Francisco Farias, Maria Cecilia Cantero, Rodolfo Feldman, Maria Carolina Ridruejo, Pedro Calella, Cesar Zaidman; **Australia:** Stephen Stranks, Peak Man Mah, Alison Nankervis, Duncan Topliss, Georgia Soldatos, Richard Simpson, Murray Gerstman, David Colquhoun, Ferdinandus De Looze, Robert Moses, Michael Suranyi, Samantha Hocking, David Packham, Duncan Cooke, Karam Kostner; **Belgium:** Eric Weber, Chris Vercammen, Luc Van Gaal, Jozef Tits, Bart Keymeulen, Chantal Mathieu; **Canada:** Naresh Aggarwal, Dan Dattani, Francois Blouin, Richard Dumas, Sam Henein, Patrick Ma, Ali Najarali, Michael Omahony, Tracy Pella, Wilson Rodger, Daniel Shu, Vincent Woo, Brian Zidel, Lew Pliamm, Brian Ramjattan, Ronald Akhras, Jasmin Belle-Isle, Stuart Ross, Geza Molnar; **Colombia:** Juan Manual Arteaga, Ivonne Jarava; **Czech Republic:** Alena Andresova, Miloslava Komrskova, Cyril Mucha, Tomas Brychta, Dagmar Bartaskova, Romana Urbanova, Tomas Spousta, Jana Havelkova, Tomas Sedlacek, Milan Kvapil; **Estonia:** Ülle Jakovlev, Verner Fogel, Liina Viitas, Mai Soots, Maire Lubi, Marju Past, Jelena Krasnopejeva; **Germany:** Hasan Alawi, Klaus Busch, Felix Klemens Pröpper, Andrea Thron, Stephan Jacob, Andreas Pfützner, Ludger Rose, Thomas Segiet, Christine Kosch, Andrea Moelle; **Great Britain:** Melanie Davies, Hamish Courtney, Martin Gibson, Luigi Gnudi, Frances Game, John Wilding, Thozhukat Sathyapalan, Miles Fisher, Shenaz Ramtoola, Satyan Rajbhandari, Maurice Okane; **Hungary:** Eleonora Beke, Ferenc Poor, Karoly Nagy, Gyozo Kocsis, Tamas Oroszlan, Peter Faludi, Mihaly Gurzo; **India:** Sathyanarayana Srikanta, Mala Dharmalingam, Bala Murugan, Pramod Gandhi, Bipin Sethi, Sosale Aravind, Sharda Ardhanareeshwaran, Arpan Bhattacharyya, Ganapathi Bantwal, Vijay Viswanathan, Paramesh Shamanna, Banshi Saboo, Viswanathan Mohan, Reshma Parmaj, Kirti Kumar Modi, Sindhu Joshi, Sunil Jain, Sanjay Kalra, Arun Chankramath Somasekharan, Prabha Adhikari, Ajay Kumar, Harshada Kudalkar, Rajiv Passey, Mathew John, Sadasivarao Yalamanchi, Keyur Parikh, K.P. Rajesh, Rajesh Nair, Ajay Kumar, Sasi Kumar, Lily Rodrigues, Pawan Gangwal, Pankaj Agarwal, Sandeep Kumar Gupta, Abhay Amrutlal Mutha, Shailaja Dilip Kale, Ravindra Laxman Kulkarni, Sandip Chudasama, Kamal Sharma, Anoop Nambiar, Aniruddha Tangaonkar, Vaishali Deshmukh, Biswakesh Majumdar, Rajendran Veerappan, Deepak Namjoshi; **Israel:** Itamar Raz, Julio Weinstein, Ilana Harman Boehm, Victor Vishlitzky; **Luxembourg:** Frederic Dadoun; **Malaysia:** Rajesh P. Shah, Lai Seong Hooi, Alexander Tan, Wan Mohamad Wan Bebakar, Mafauzy Mohamed, Amir S. Khir, Norlela Sukor, Khalid Abdul Kadir; **Mexico:** Enrique Morales, Sergio Zuñiga, Melchor Alpizar, Cesar Calvo, Rolando Zamarripa, Juan Rosas, Armando Vargas; **The Netherlands:** Max Nieuwdorp, Vicdan Kose, Susanne Kentgens, Gloria Rojas, Wouter Van Kempen, Jacqueline Hoogendijk, Mazin Alhakim, Victor Gerdes, Marcel Hovens, Johan Berends, A. Woittiez, Cees Jan Smit, B. Dekkers, Wilco Spiering, Marcel K. Van Dijk-Okla, Ben P.M. Imholz, Ruud J.M. Van Leendert, Marije Ten Wolde, Peter J.H. Smak Gregoor; **New Zealand:** Russell Scott, Jeremy Krebs, John Baker, Joe Singh, Calum Young; **Norway**: Gisle Langslet, Hans Olav Hoivik, Torbjorn Kjaernli, Sigbjorn Elle, Eric Gjertsen, Knut Risberg, Andreas Tandberg, Leidulv Solnoer, Per Anton Sirnes; **Poland:** Tadeusz Derezinski, Malgorzata Arciszewska, Edward Franek, Ewa Szyprowska, Dariusz Sowinski, Robert Petryka, Beata Czakanska-Dec, Grazyna Pulka, Katarzyna Jusiak, Mariusz Dabrowski, Piotr

Kubalski, Malgorzata Wojciechowska, Andrzej Madej, Danuta Pupek-Musialik; **Russia:** Natalia Blinova, Ludmila Kondratjeva, Anatoly Kuzin, Mikhail Boyarkin, Tatyana Gomova, Alexander Khokhlov, Sergey Vorobjev, Olga Mirolyubova, Svetlana Boldueva, Olga Ershova, Marina Ballyzek, Olga Smolenskaya, Sergey S. Yakushin, Dmitry Zateyshchikov, Mikhail Arkhipov, Alexandr Kuzmenko, Ivan Maksimov, Igor Motylev, Vladimir Rafalskiy, Leonid Strongin, Tatyana Treshkur, Natalya Volkova, Olga Barbarash, Tatiana Raskina, Leonid Bartosh, Inna Nikolskaya, Elena Shutemova, Viktor Gurevich, Natalia Burova, Elena Vorobyeva, Denis Andreev, Boris Bart, Tatiana Khlevchuk, Lyudmila Gapon, Ivan Gordeev, Nikolai Gratsiansky, Alsu Zalevskaya, Sergey Sayganov, Oleg Solovyev, Galina Reshedko, Natalia Shilkina, Petr Chizhov, Julia Shapovalova, Alexander Sherenkov, Olga Reshetko, Vladimir Simanenkov; **Spain:** Juan Garcia Puig, Jose Saban, Jose Pascual, Jose Dominguez, Elias Delgado, Carlos Calvo, Manuel Vida, Santiago Duran, Francisco Tinahones, Jordi Salas, Jose Miguel Gonzalez, Manuel Monreal, Armand Grau, Andreu Nubiola, Pere Alvarez; **Sweden:** Kaj Stenlöf, Pekka Koskinen, Carl-Johan Lindholm, Ulrik Mathiesen, Katarina Berndtsson Blom, Bengt-Olov Tengmark, Hans Jul-Nielsen; **Ukraine:** Oleksandr Larin, Svetlana Panina, Svitlana Kovalenko, Olena Voloshyna, Vera Tseluyko, Olga Gyrina, Vadim Vizir, Olga Barna, Maryna Dolzhenko, Yuriy Mostovoy, Vadim Korpachev, Boris Mankovskiy, Mykola Vatutin; **United States:** Charles Arena, Basil Akpunonu, Rahfa Zerikly, Claire Baker, Toby Briskin, Darlene Bartilucci, Joshua Barzilay, Christian Breton, John Buse, Richard Cherlin, Michael Cobble, Clarence Ellis, Raymond Fink, Alan Forker, Ronald Garcia, Priscilla Hollander, Angela House, Daniel Hyman, Richard Ingebretsen, David Jack, Judith Kirstein, Kerri Kissell, Daniel Lorber, Donald McNeil, Wendell Miers, Alex Murray, Robert Call, Stephen T. Ong, Fernando Ovalle, Robert Pearlstein, Veronica Piziak, Daniel Pomposini, David Robertson, Julio Rosenstock, Ulrich Schubart, Shaukat Shah, Rodney Stout, Mark Turner, James Wallace, Leonard Chuck, Edmund Claxton, Emily Morawski, Alan Wynne, Carol Wysham, Michael Alderman, Walter Patton, Bryan Pogue, Arnold Silva, Roger Guthrie, Sam Lerman, Robert Madder, Wendy Miller, Daniel Weiss, Dean Kereiakes, Ronald J Graf, Negah Rassouli, James Greenwald, Hanna Abu-Nassar, Derek Muse, Vicki Kalen, Natalia Hegedosh, Richard Dobrusin, Glover Johnson, Tami Bruce, Gary Gleason.

CANVAS-R

Argentina: Marisa Vico, Sonia Hermida, Lucrecia Nardone, Laura Maffei, Javier Farias, Elizabeth Gelersztein, Maximiliano Sicer, Andres Alvarisqueta, Georgina Sposetti, Virginia Visco, Rodolfo Feldman, Silvia Orio; **Australia:** Christopher Nolan, Michael Suranyi, Samantha Hocking, Stephen Stranks, Duncan Cooke, Ferdinandus de Looze, Ashim Sinha, Timothy Davis, Anthony Russell, Acharya Shamasunder, Murray Gerstman, Richard MacIsaac; **Belgium:** Chris Vercammen, Luc Van Gaal, Chantal Mathieu, Xavier Warling, Jan Behets, Andre Scheen, Guy T'Sjoen, Ann Verhaegen, Isabelle Dumont, Youri Taes, Francis Duyck, Fabienne Lienart; **Brazil:** Adolfo Sparenberg, Adriana Costa e Forti, Andressa Leitao, Cariolina Jungers di Siqueira Chrisman, César Hayashida, Daniel Panarotto, Fabio Rossi dos Sanos, Fadlo Fraige Filho, Flávia Coimbra Maia, Gilmar Reis, Hugo Lisboa, Joao Felicio, Joselita Siqueira, Lilia Nigro Maia, Luiz Alberto Andreotti Turatti, Maria José Cerqueira, Maria Tereza Zanella, Patricia Muszkat, Miguel Nasser Hissa, Teresa Bonansea; **Canada:** Igor Wilderman, Vincent Woo, Richard Dumas, Francois Blouin, Pierre Filteau, George Tsoukas, Peter Milne, Dan Dattani, Chantal Godin, Michael Omahony, Daniel Shu, Jasmin Belle-Isle, Douglas Friars, Anil Gupta, Ted Nemtean, Andrew Steele; **China:** Zhan-Quan Li, Changsheng Ma, Linong Ji, Shuguang Pang, Yan Jing,

Ruiping Zhao, Ruifang Bu; **Czech Republic:** Tomas Spousta, Tatana Souckova, Dagmar Bartaskova, Pavlina Kyselova, Lea Raclavska, Milan Kvapil, Jana Havelkova, Emilia Malicherova; **France:** Philippe Zaoui, Didier Gouet, Jean-Pierre Courreges, Salha Fendri, Samy Hadjadj, Bruno Verges, Bogdan Nicolescu Catargi, Sylvaine Clavel, Jean-Jacques Altman, Agnes Hartemann, Gaétan Prevost; **Germany:** Diethelm Tschöpe, Elena Henkel, Rolf Göbel, Jochen Seufert, Hermann Haller, Thomas Behnke, Andreas Pfützner, Gerhard Klausmann, Klaus Busch, Baerbel Hirschhaeuser, Stephan Jacob; **Great Britain:** Melanie Davies, Rob Andrews, Narayan Annamalai, Hamish Courtney, Srikanth Bellary, Mark Blagden, John Clark, Steven Creely, Ken Darzy, Iskandar Idris, Richard Falk, Lucinda Summers, Njaimeh Asamoah, Andrew Johnson, See Kwok, Shenaz Ramtoola, Gerry Rayman, Jamie Smith, John Wilding; **Hungary:** Marietta Baranyai, Katalin Csomos, Mihaly Gurzo, Eleonóra Harcsa, Nikosz Kanakaridisz, Nóra Késmárki, Tamas Oroszlan, József Pátkay, Eva Peterfai, Balázs Gaszner, Ildiko Jozsef; **Italy:** Stefano Genovese, Antonio Ettore Pontiroli, Enzo Bonora, Dario Giugliano, Domenico Cucinotta, Giorgio Sesti, Paola Ponzani, Giuseppe Pugliese, Giulio Marchesini Reggiani, Paolo Pozzilli, Sergio Leotta, Emanuela Orsi, Carlo Giorda, Paolo Di Bartolo; **Korea:** Tae-Sun Park, Chung-Gu Cho, In-Joo Kim, Il Seong Nam-Goong, Choon Hee Chung, Ho Chan Cho, Dong-Seop Choi, Kun-Ho Yoon, Nan-Hee Kim, Kyung-Mook Choi, Kyu-Jeung Ahn, Ji-Oh Mok, Soon-Jib Yoo, Tae-Keun Oh, Kwan-Woo Lee, Hak-Chul Jang, Jeong-Hyun Park, In-Kyu Lee, Byung-Joon Kim, Doo-Man Kim, Ho Sang Shon, Moon-Kyu Lee, ShinGon Kim; **Malaysia:** Mafauzy Mohamed, Paranthaman Vengadasalam, Alexander Tong Boon Tan, Wan Mohd Izani Wan Mohamed, Rajesh P Shah, Khalid Yusoff, Amir Sharifuddin Mohd Khir, Florence Tan, Mansor Yahya; **Mexico:** Rafael Violante, Manuel Odin De los Rios, Marco Alcocer, Enrique Morales, Juan Rosas, Armando Vargas, Manuel González, Esperanza Martinez, Jorge Antonio Aldrete, Guillermo Gonzalez, Cynthia Mustieles Rocha, Leobardo Sauque, Paul Frenk, José Luis Arenas; **The Netherlands:** Peter Tichelaar, A Kooy, Albert Van de Wiel, Gerben Lochorn, Peter De Vries, Hans Feenstra, Max Nieuwdorp, Wouter Van Kempen, Mazin Alhakim, Ben Imholz, Ruud van Leendert, Peter Smak Gregoor, Joop Brussen, Hanno Pijl, Manuel Castro Cabezas, F Gonkel, P Smits, Daan Lansdorp, Susanne Kentgens, Aletha Veenendaal, Gloria Rojas; **New Zealand:** John Richmond, Russell Scott, Mike Williams, Dean Quinn, Jeremy Krebs, John Baker, Veronica Crawford, Calum Young; **Poland:** Malgorzata Arciszewska, Krystyna Jedynasty, Dariusz Sowinski, Ewa Szyprowska, Andrzej Madej, Miroslawa Polaszewska-Muszynska, Danuta Zytkiewicz-Jaruga, Katarzyna Wasilewska, Piotr Romanczuk, Anna Ocicka-Kozakiewicz, Czeslaw Marcisz, Boguslaw Okopien, Anna Bochenek, Lukasz Wojnowski, Teresa Sliwinska, Barbara Rewerska, Witold Zmuda, Katarzyna Klodawska, Ewa Skokowska, Jacek Fabisiak, Cezary Danilkiewicz; **Puerto Rico**: Elba Perez Vargas, Elizabeth Barranco Santana; **Russia**: Tatiana Raskina, Olga Barbarash, Leonid Bartosh, Igor Motylev, A Kuzin, Olga Reshetko, Tatyana Zykova, Olga Ershova, Marina Balyzek, Vladimir Rafalsky, Natalya Volkova, Nina Nosova, Natalia Burova, Alsu Zalevskaya, Galina Reshedko, Natalia Shilkina, Petr Chizhov, Alexander Sherenkov, Vladimir Simanenkov, Tatiana Lysenko, Irina Ipatko, Mikhail Boyarkin, Sergey Vorobyev, Lyudmila Gapon, Andrey Obrezan, Valeria Esip, Zhanna Paltsman, Andrey Verbovoy, Fatima Khetagurova, Yuri Shvarts; **Spain:** Pere Alvarez-Garcia, Francisco Martinez Deben, Josep M Grinyo, Carlos Calvo, Carmen Suarez, JM Pascual, Jose Dominguez, Anna Oliveras, Armand Grau, Fernando Gómez Peralta, Luis Alvarez-Sala, Cañizo Francisco, Jorge Gómez Cerezo, Juan Garcia Puig, Carlos Trescolí, Francisco Jose Fuentes Jimenez, Santiago Tofé, Judith López, Javier Nieto Iglesias, Luis Vigil, Santiago Duran Garcia, Jose Luis Gorriz, Pilar Saavedra Vallejo, Francisco Tinahones Madueno, Jose Luis Blanco Coronado, Alfonso Soto, Luis De Teresa, Jose Miguel Gonzalez, Antonio Rodriguez Botaro, Carmina Cuesta; **Sweden:** Bjorn

Bragée, Bengt-Olov Tengmark, Hans Jul-Nielsen, Pekka Koskinen, Linda Moris, Fredrik Huss, Pär Jennersjö, Katarina Berndtsson-Blom, Bo Liu, Kaj Stenlöf, Carl-Johan Lindholm, Johan Jendle; **Taiwan:** Dee Pei, Wayne H-H Shue, Chern-En Chiang, Ching-Chu Chen, Ming-Nan Chien, Ping-Yen Liu, Ching-Ling Lin, Yi-Jing Sheen; **Ukraine:** Dmytro Reshotko, Nikolay Rishko, Olexander Samoylov, Valentina Serkova, Ivan Smirnov, Liubov Sokolova, Vira Tseluyko, Vadym Vizir, Tetiana Zlova, Vitaliy Maslyanko, Oleksandr Larin, Valentina Velichko, Lyudmila Prystupa, Nadiya Yarema, Galina Mishanich, Iryna Bondarets, Nataliya Virstyuk, Olexander Serhiyenko, Stepan Pavlyk, Olena Levchenko, Orest Abrahamovych, Volodymyr Botsurko, Maryna Dolzhenko, Victoria Chernikova, Yuriy Karachentsev, Vitaliy Katerenchuk, Vadym Korpachov, Yaroslav Malynovsky, Boris Mankovsky, Yuriy Mostovoy, Larisa Pererva, Nataliya Pertseva; **United States:** Vicki Conrad, Kenneth Fox, David Jack, Robert Buynak, Michael Dever, John Kirby, Larry Odekirk, Priyantha Wijewardane, Robert Carson, Bruce Seaton, Ann Elizabeth Mohart, Salvatore Bianco, Michael R Cox, Andrew Kim, Steven Geller, Jakkidi Reddy, Derek Muse, Alan Wynne, Harold Bays, Judith Kirstein, James Riser, Ahmed Arif, Claire Baker, Kim Barbel-Johnson, Gary Bedel, Pierre Blemur, Christian Breton, Anna Chang, Brian Naccari, Nancy Jo Coburn, Lisa Cohen, Eric Dedeke, Charles Diederich, John Earl, Anu George, Matthew Gilbert, Gary Gleason, Gregory Haase, Rodney Ison, Mahendra Jain, Imtiaz Alam, Sam Lerman, Lawrence Levinson, Lon D Lynn, Michael Oliver, Barry Kusnick, Robert Pearlstein, Sanford Plevin, Samuel Mujica Trenche, Vernon Young, Michael Jutovsky, Ralph Wade, James Wallace, Albert Weisbrot, Duane Wombolt, Alan Forker, Jalal Taslimi, Roger Guthrie.

CANVAS Program committees

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CANVAS Program cardiovascular, renal, and cause of death criteria

A. Death

All deaths will be reviewed by the adjudicators. Because the main role is to identify cardiovascular deaths, the approach used will be to present all deaths as potential cardiovascular deaths and ask the committee to confirm or refute that the cause was cardiovascular. Because there is often confusion in reporting cause of death, the study will seek a proximate cause and underlying cause(s) of death in every case (although it is understood that it may not be possible to assign both for all deaths). The question about cardiovascular cause will be applied jointly to the proximate and underlying causes. The reason for assigning a death as cardiovascular or noncardiovascular, and the reasoning behind the adjudicator's assignment of the cause of death, will be documented.

The determination of the specific cause of cardiovascular death is complicated by the fact that the interest is particularly in one underlying cause of death (acute myocardial infarction [MI] and several modes of death (arrhythmia and heart failure/low output). It is noted that heart attack–related deaths are manifested as sudden death or heart failure, so these events need to be carefully defined.

Definition of Cardiovascular Death

Cardiovascular death includes death resulting from an acute MI, sudden cardiac death, death due to heart failure, death due to stroke, and death due to other cardiovascular causes, as follows:

1. **Death Due to Acute MI** refers to a death by any mechanism (arrhythmia, heart failure [HF], low output) within 30 days after a MI related to the immediate consequences of the myocardial infarction, such as progressive congestive heart failure (CHF), inadequate cardiac output, or recalcitrant arrhythmia. If these events occur after a "break" (e.g., a CHF- and arrhythmia-free period of at least a week), they should be designated by the immediate cause, even though the MI may have increased the risk of that event (e.g., late arrhythmic death becomes more likely after an acute MI). The acute MI should be verified to the extent possible by the diagnostic criteria outlined for acute MI or by autopsy findings showing recent MI or recent coronary thrombus. Sudden cardiac death, if accompanied by symptoms suggestive of myocardial ischemia, new ST elevation, new left bundle branch block (LBBB), or evidence of fresh thrombus by coronary angiography and/or at autopsy should be considered death resulting from an acute MI, even if death occurs before blood samples or 12-lead electrocardiogram (ECG) could be obtained, or at a time before the appearance of cardiac biomarkers in the blood. Death resulting from a procedure to treat a MI (percutaneous coronary intervention [PCI], coronary artery bypass graft surgery [CABG]), or to treat a complication resulting from MI, should also be considered death due to acute MI.

   Death resulting from a procedure to treat myocardial ischemia (angina) or death due to a MI that occurs as a direct consequence of a cardiovascular

investigation/procedure/operation should be considered as a death due to other cardiovascular causes.

2. **Sudden Cardiac Death** refers to a death that occurs unexpectedly, not following an acute MI, and includes the following deaths:
   a. Death witnessed and instantaneous without new or worsening symptoms
   b. Death witnessed within 60 minutes of the onset of new or worsening cardiac symptoms, unless the symptoms suggest acute MI
   c. Death witnessed and attributed to an identified arrhythmia (e.g., captured on an ECG recording, witnessed on a monitor, or unwitnessed but found on implantable cardioverter-defibrillator review)
   d. Death after unsuccessful resuscitation from cardiac arrest
   e. Death after successful resuscitation from cardiac arrest and without identification of a noncardiac etiology (postcardiac arrest syndrome)
   f. Unwitnessed death without other cause of death (information regarding the patient's clinical status preceding death should be provided, if available)

   General Considerations
   - A subject seen alive and clinically stable 12-24 hours prior to being found dead without any evidence or information of a specific cause of death should be classified as "sudden cardiac death." Typical scenarios include:
     - Subject well the previous day but found dead in bed the next day
     - Subject found dead at home on the couch with the television on
   - Deaths for which there is no information beyond "Patient found dead at home" may be classified as "death due to other cardiovascular causes" or in some trials, "undetermined cause of death." Please see *Definition of Undetermined Cause of Death*, for full details.

3. **Death Due to HF or Cardiogenic Shock** refers to a death occurring in the context of clinically worsening symptoms and/or signs of heart failure without evidence of another cause of death and not following an acute MI. Note that deaths due to HF can have various etiologies, including one or more acute MIs (late effect), ischemic or nonischemic cardiomyopathy, or valve disease.

   Death due to HF or Cardiogenic Shock should include sudden death occurring during an admission for worsening heart failure as well as death from progressive HF or cardiogenic shock following implantation of a mechanical-assist device.

   New or worsening signs and/or symptoms of CHF include any of the following:
   a. New or increasing symptoms and/or signs of HF requiring the initiation of, or an increase in, treatment directed at HF or occurring in a patient already receiving maximal therapy for HF
   b. HF symptoms or signs requiring continuous intravenous therapy or chronic oxygen administration for hypoxia due to pulmonary edema
   c. Confinement to bed predominantly due to HF symptoms
   d. Pulmonary edema sufficient to cause tachypnea and distress **not** occurring in the

context of an acute MI, worsening renal function, or as the consequence of an arrhythmia occurring in the absence of worsening heart failure

e. Cardiogenic shock **not** occurring in the context of an acute MI or as the consequence of an arrhythmia occurring in the absence of worsening HF

   Cardiogenic shock is defined as systolic blood pressure (SBP) <90 mmHg for greater than 1 hour, not responsive to fluid resuscitation and/or heart rate correction, and felt to be secondary to cardiac dysfunction and associated with at least one of the following signs of hypoperfusion:
   - Cool, clammy skin ***or***
   - Oliguria (urine output <30 ml/hour) ***or***
   - Altered sensorium ***or***
   - Cardiac index <2.2 l/min/m^2

   Cardiogenic shock can also be defined if SBP <90 mmHg and increases to ≥90 mmHg in less than 1 hour with positive inotropic or vasopressor agents alone and/or with mechanical support.

General Considerations

HF may have a number of underlying causes, including acute or chronic ischemia, structural heart disease (e.g., hypertrophic cardiomyopathy), and valvular heart disease. Where treatments are likely to have specific effects, and it is likely to be possible to distinguish between the various causes, then it may be reasonable to separate out the relevant treatment effects. For example, obesity drugs such as fenfluramine (pondimin) and dexfenfluramine (redux) were found to be associated with the development of valvular heart disease and pulmonary hypertension. In other cases, the aggregation implied by the definition above may be more appropriate.

4. **Death Due to Stroke** refers to death occurring up to 30 days after a stroke that is either due to the stroke or caused by a complication of the stroke.

5. **Death Due to Other Cardiovascular Causes** refers to a cardiovascular death not included in the above categories (e.g., dysrhythmia unrelated to sudden cardiac death, pulmonary embolism, cardiovascular intervention [other than one related to an acute MI], aortic aneurysm rupture, or peripheral arterial disease). Mortal complications of cardiac surgery or nonsurgical revascularization should be classified as cardiovascular deaths.

Definition of Noncardiovascular Death

Noncardiovascular death is defined as any death that is not thought to be due to a cardiovascular cause. Detailed recommendations on the classification of noncardiovascular causes of death are beyond the scope of this document. The level of detail needed and the optimum classification will depend on the nature of the study population and the anticipated number and type of noncardiovascular deaths. Any specific anticipated safety concern should be included as a separate cause of death. The following is a suggested list of noncardiovascular* causes of death:

1. **Nonmalignant Causes**
   - Pulmonary
   - Renal
   - Gastrointestinal
   - Hepatobiliary
   - Pancreatic
   - Infection (includes sepsis)
   - Noninfectious (e.g., systemic inflammatory response syndrome [SIRS])
   - Hemorrhage, not intracranial
   - Noncardiovascular system organ failure (e.g., hepatic failure)
   - Noncardiovascular surgery
   - Other noncardiovascular, specify: _____
   - Accidental/Trauma
   - Suicide
   - Drug overdose

   * Death due to a gastrointestinal bleed should **not** be considered a cardiovascular death.

2. **Malignant Causes**

   Malignancy should be coded as the cause of death if:
   - Death results directly from the cancer; or
   - Death results from a complication of the cancer (e.g., infection, complication of surgery/chemotherapy/radiotherapy); or
   - Death results from withdrawal of other therapies because of concerns relating to the poor prognosis associated with the cancer.

   Cancer deaths may arise from cancers that were present prior to randomization or which developed subsequently. It may be helpful to distinguish these 2 scenarios (i.e., worsening of prior malignancy, new malignancy).

   Suggested categorization includes common organ systems, hematologic, or unknown.

Definition of Undetermined Cause of Death

Undetermined Cause of Death refers to a death not attributable to one of the above categories of cardiovascular death or to a noncardiovascular cause. Inability to classify the cause of death may be due to lack of information (e.g., the only available information is "patient died") or when there is insufficient supporting information or detail to assign the cause of death. In general, the use of this category of death should be discouraged and should apply to a minimal number of patients in well-run clinical trials.

A common analytic approach for cause of death analyses is to assume that all undetermined cases are included in the cardiovascular category (e.g., presumed cardiovascular death, specifically "death due to other cardiovascular causes"). Nevertheless, the appropriate classification and analysis of undetermined causes of death depends on the population, the intervention under investigation, and the disease process.

B. Myocardial Infarction

A nonfatal MI is an event that meets the definition below and does not result in death within 30 days from onset.

1. General Considerations

The term MI should be used when there is evidence of myocardial necrosis in a clinical setting consistent with myocardial ischemia.

In general, the diagnosis of MI requires the combination of:

- Evidence of myocardial necrosis (either changes in cardiac biomarkers or postmortem pathological findings); and
- Supporting information derived from the clinical presentation, ECG changes, or the results of myocardial or coronary artery imaging

The totality of the clinical, ECG, and cardiac biomarker information should be considered to determine whether or not a MI has occurred. Specifically, timing and trends in cardiac biomarkers and ECG information require careful analysis. The adjudication of MI should also take into account the clinical setting in which the event occurs. MI may be adjudicated for an event that has characteristics of a MI but which does not meet the strict definition because biomarker or ECG results are not available. Likewise, the committee may consider information based on its source and its likely reliability without requiring a specific source document; for example, if there is a note from a specialist that "troponins are increased" or "ECG suggests acute MI", additional documentation is generally not necessary.

2. Criteria for MI

a. Clinical Presentation

The clinical presentation should be consistent with diagnosis of myocardial ischemia and infarction. Other findings that might support the diagnosis of MI should be taken into account because a number of conditions are associated with elevations in cardiac biomarkers (e.g., trauma, surgery, pacing, ablation, CHF, hypertrophic cardiomyopathy, pulmonary embolism, severe pulmonary hypertension, stroke or subarachnoid hemorrhage, infiltrative and inflammatory disorders of cardiac muscle, drug toxicity, burns, critical illness, extreme exertion, and chronic kidney disease). Supporting information can also be considered from myocardial imaging and coronary imaging. The totality of the data may help differentiate acute MI from the background disease process.

b. Biomarker Elevations

For cardiac biomarkers, laboratories should report an upper reference limit (URL). If the 99th percentile of the URL from the respective laboratory performing the assay is not available, then the URL for myocardial necrosis from the laboratory should be used. If the 99th percentile of the URL or the URL for myocardial necrosis is not available, the MI decision limit for the particular laboratory should be used as the URL. Laboratories can also report both the 99th percentile of the upper reference

limit and the MI decision limit. Reference limits from the laboratory performing the assay are preferred over the manufacturer's listed reference limits in an assay's instructions for use. Creatine-kinase (CK)-MB and troponin are preferred, but CK may be used in the absence of CK-MB and troponin.

For MI subtypes, different biomarker elevations for CK, CK-MB, or troponin will be important sources of information. The specific criteria will be referenced to the URL.

In many studies, particularly those in which patients present acutely to hospitals that are not participating sites, it is not practical to stipulate the use of a single biomarker or assay, and the locally available results are to be used as the basis for adjudication. However, if possible, using the same cardiac biomarker assay and preferably, a core laboratory, for all measurements reduces interassay variability.

Since the prognostic significance of different types of MIs (e.g., periprocedural MI versus spontaneous MI) may be different, consider evaluating outcomes for these subsets of patients separately.

c. Electrocardiogram (ECG) Changes

ECG changes can be used to support or confirm an MI. Supporting evidence may be ischemic changes, and confirmatory information may be new Q waves.

- **Criteria for acute myocardial ischemia (in absence of left ventricular hypertrophy [LVH] and LBBB):**
  - ST elevation
  - New ST elevation at the J point in 2 anatomically contiguous leads with the cut-off points: ≥0.2 mV in men (>0.25 mV in men <40 years) or ≥0.15 mV in women in leads V2-V3 and/or ≥0.1 mV in other leads.
  - ST depression and T wave changes
  - New horizontal or down-sloping ST depression ≥0.05 mV in 2 contiguous leads; and/or new T inversion ≥0.1 mV in 2 contiguous leads.

  The above ECG criteria illustrate patterns consistent with myocardial ischemia. In patients with abnormal biomarkers, it is recognized that lesser ECG abnormalities may represent an ischemic response and may be accepted under the category of abnormal ECG findings.
- **Criteria for pathological Q wave**
  - Any Q-wave in leads V2-V3 ≥0.02 seconds or QS complex in leads V2 and V3
  - Q-wave ≥0.03 seconds and ≥0.1 mV deep or QS complex in leads I, II, aVL, aVF, or V4-V6 in any two leads of a contiguous lead grouping (I, aVL, V6; V4-V6; II, III, and aVF). (The same criteria are used for supplemental leads V7-V9, and for the Cabrera frontal plane lead grouping.)
- **Criteria for prior MI**
  - Pathological Q waves, as defined above
  - R-wave ≥0.04 seconds in V1-V2 and R/S ≥1 with a concordant positive T-wave in the absence of a conduction defect

3. MI Subtypes

Several MI subtypes are commonly reported in clinical investigations and each is defined below:

a. Spontaneous MI

1) Detection of rise and/or fall of cardiac biomarkers with at least one value above the URL with at least one of the following:
   - Clinical presentation consistent with ischemia
   - ECG evidence of acute myocardial ischemia
   - New pathological Q waves
   - Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality
   - Autopsy evidence of acute MI
2) If biomarkers are elevated from a prior infarction, then a spontaneous MI is defined as:
   a) One of the following:
      - Clinical presentation consistent with ischemia
      - ECG evidence of acute myocardial ischemia
      - New pathological Q waves
      - Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality
      - Autopsy evidence of acute MI

   AND

   b) Both of the following:
      - Evidence that cardiac biomarker values were decreasing (e.g., 2 samples 3-6 hours apart) prior to the suspected MI (if biomarkers are increasing or peak is not reached, then a definite diagnosis of recurrent MI is generally not possible)
      - ≥20% increase (and >URL) in troponin or CK-MB between a measurement made at the time of the initial presentation and a further sample taken 3-6 hours later

b. PCI-related MI

Peri-PCI MI is defined by any of the following criteria. Symptoms of cardiac ischemia are not required.

1) Biomarker elevations within 48 hours of PCI:
   - Troponin or CK-MB (preferred) >3 × URL **AND**
   - No evidence that cardiac biomarkers were elevated prior to the procedure;

OR

   - Both of the following must be true:
     - ≥50% increase in the cardiac biomarker result (data should be collected in such a way that analyses using ≥20% or ≥50% could both be performed)
     - Evidence that cardiac biomarker values were decreasing (e.g., 2 samples 3-6 hours apart) prior to the suspected MI
2) New pathological Q waves
3) Autopsy evidence of acute MI

c. CABG-Related MI

Peri-CABG MI is defined by the following criteria. Symptoms of cardiac ischemia are not required.

1) Biomarker elevations within 72 hours of CABG:
   - Troponin or CK-MB (preferred) >5 × URL ***AND***
   - No evidence that cardiac biomarkers were elevated prior to the procedure;

OR

   - Both of the following must be true:
     - ≥50% increase in the cardiac biomarker result (data should be collected in such a way that analyses using ≥20% or ≥50% could both be performed)
     - Evidence that cardiac biomarker values were decreasing (e.g., 2 samples 3-6 hours apart) prior to the suspected MI.

AND

2) One of the following:
   - New pathological Q waves persistent through 30 days
   - New persistent non–rate-related LBBB
   - Angiographically documented new graft or native coronary artery occlusion
   - Other complication in the operating room resulting in loss of myocardium
   - Imaging evidence of new loss of viable myocardium

OR

3) Autopsy evidence of acute MI

4. Clinical Classification of Different Types of MI

a. Particular categories of MI will be distinguished using the following guidelines:

- Type 1
  Spontaneous MI related to ischemia due to a primary coronary event such as plaque erosion and/or rupture, fissuring, or dissection
- Type 2
  MI secondary to ischemia due to either increased oxygen demand or decreased supply (e.g., coronary artery spasm, coronary embolism, anemia, arrhythmias, hypertension, or hypotension)
- Type 3
  Sudden unexpected cardiac death, including cardiac arrest, often with symptoms suggestive of myocardial ischemia, accompanied by presumably new ST elevation, or new LBBB, or evidence of fresh thrombus in a coronary artery by angiography and/or at autopsy, but death occurring before blood samples could be obtained, or at a time before the appearance of cardiac biomarkers in the blood
- Type 4a
  MI associated with PCI
- Type 4b
  MI associated with stent thrombosis as documented by angiography or at autopsy
- Type 5
  MI associated with CABG

b. For each MI identified, the type of MI will also be described as:

- ST-Elevation MI (STEMI)
    - Also categorize as:
        - Q wave
        - Non–Q wave
        - Unknown (no ECG or ECG not interpretable)
- Non-ST-Elevation MI (NSTEMI)
    - Also categorize as:
        - Q wave
        - Non–Q wave
        - Unknown (no ECG or ECG not interpretable)
- Unknown (no ECG or ECG not interpretable)

C. Stroke

A nonfatal stroke is an event that meets the current classification definition below and does not result in death within 30 days from onset. Stroke will also be classified by the EAC according to historical criteria. Any recurrence or exacerbation of the condition within 30 days is considered part of the original episode, whereas beyond that time period it is considered a separate event.

Transient Ischemic Attack

Transient ischemic attack (TIA) is defined as a transient episode of neurological dysfunction caused by focal brain, spinal cord, or retinal ischemia, *without* acute infarction.

The distinction between a TIA and an ischemic stroke is the presence of infarction, not the transience of the symptoms. In addition to laboratory documentation of infarction, persistence of symptoms is an acceptable indicator of infarction. Thus, symptoms lasting ≤24 hours versus >24 hours may be used by the EAC to distinguish between transient ischemia and infarction. The committee will endeavor to review any relevant documentation of the cerebrovascular event. However, in the absence of documentation regarding duration of the symptoms, the committee may on occasion use any other reliable source of information such as the diagnosis of the treating physician to determine if the event was a TIA or stroke.

Stroke

1. Historical classification
   An acute disturbance of focal neurological function resulting in symptoms lasting more than 24 hours.
2. Current classification
   Stroke is defined as an acute episode of neurological dysfunction caused by focal or global brain, spinal cord, or retinal vascular injury.
   a. Ischemic stroke
      Ischemic stroke is defined as an acute episode of focal cerebral, spinal, or retinal dysfunction caused by an infarction of central nervous system tissue.
      Hemorrhage may be a consequence of ischemic stroke. In this situation, the stroke is an ischemic stroke with hemorrhagic transformation and not a hemorrhagic stroke.

b. Hemorrhagic stroke
   Hemorrhagic stroke is defined as an acute episode of focal or global cerebral or spinal dysfunction caused by a nontraumatic intraparenchymal, intraventricular, or subarachnoid hemorrhage.
c. Undetermined stroke
   Undetermined stroke is defined as a stroke with insufficient information to allow categorization as ischemic or hemorrhagic.

General Considerations

Evidence of vascular central nervous system injury without recognized neurological dysfunction may be observed. Examples include microhemorrhage, silent infarction, and silent hemorrhage. When encountered, the clinical relevance of these findings may be unclear. If observed, they should be precisely defined and categorized by the EAC.

D. Hospitalized Congestive Heart Failure

HF requiring hospitalization is defined as an event that meets the following criteria:

1. Requires hospitalization defined as an admission to an inpatient unit or a visit to an emergency department that results in at least a 24-hour stay (or a date change if the time of admission/discharge is not available).
   AND
2. Clinical symptoms of HF, including ≥1 of the following new or worsening conditions:
   - Dyspnea
   - Orthopnea
   - Paroxysmal nocturnal dyspnea
   - Increasing fatigue/worsening exercise tolerance

   AND
3. Physical signs of HF, including ≥2 of the following:
   - Edema (greater than 2+ lower extremity)
   - Pulmonary crackles greater than basilar (pulmonary edema must be sufficient to cause tachypnea and distress not occurring in the context of an acute MI or as the consequence of an arrhythmia occurring in the absence of worsening HF)
   - Jugular venous distension
   - Tachypnea (respiratory rate >20 breaths/minute)
   - Rapid weight gain
   - S3 gallop
   - Increasing abdominal distension or ascites
   - Hepatojugular reflux
   - Radiological evidence of worsening HF
   - A right heart catheterization within 24 hours of admission showing a pulmonary capillary wedge pressure (pulmonary artery occlusion pressure) ≥18 mmHg or a cardiac output <2.2 l/min/m^2

   Note: biomarker results (e.g., brain natriuretic peptide [BNP]) consistent with CHF will be supportive of this diagnosis, but the elevation in BNP cannot be due to other

conditions such as cor pulmonale, pulmonary embolus, primary pulmonary hypertension, or congenital heart disease. Increasing levels of BNP, although not exceeding the ULN, may also be supportive of the diagnosis of CHF in selected cases (e.g., morbid obesity).

AND

4. Need for additional/increased therapy
   - Initiation of, or an increase in, treatment directed at HF or occurring in a patient already receiving maximal therapy for HF and including ≥1 of the following:
     - Initiation of or a significant augmentation in oral therapy for the treatment of CHF
     - Initiation of intravenous diuretic, inotrope, or vasodilator therapy
     - Up-titration of intravenous therapy, if already on therapy
     - Initiation of mechanical or surgical intervention (mechanical circulatory support, heart transplantation or ventricular pacing to improve cardiac function), or the use of ultrafiltration, hemofiltration, or dialysis that is specifically directed at treatment of HF.

AND

5. No other noncardiac etiology (such as chronic obstructive pulmonary disease, hepatic cirrhosis, acute renal failure, or venous insufficiency) and no other cardiac etiology (such as pulmonary embolus, cor pulmonale, primary pulmonary hypertension, or congenital heart disease) for signs or symptoms is identified.

   Note: it is recognized that some patients may have multiple simultaneous disease processes. Nevertheless, for the endpoint event of HF requiring hospitalization, the diagnosis of CHF would need to be the primary disease process accounting for the above signs and symptoms.

E. Renal endpoints

The renal endpoints of interest are:

- Progression of albuminuria;
- Regression of albuminuria;
- Renal composites:
  - 40% decrease in estimated glomerular filtration rate (eGFR), renal death, or requirement for renal replacement therapy;

Albuminuria

Urinary albumin:creatinine ratio (ACR) is used to assess albuminuria. Subjects will be classified as having normoalbuminuria (ACR <30 mg/g), microalbuminuria (ACR ≥30 mg/g and ≤300 mg/g), or macroalbuminuria (ACR >300 mg/g).

- **Albuminuria progression** is the development of microalbuminuria or macroalbuminuria in a subject with baseline normoalbuminuria or the development of macroalbuminuria in a subject with baseline microalbuminuria, accompanied by an ACR value increase of greater than or equal to 30% from baseline.
- **Albuminuria regression** is the development of normoalbuminuria in a subject with baseline microalbuminuria or macroalbuminuria or the development of

microalbuminuria in a subject with baseline macroalbuminuria, accompanied by a decrease in the urinary ACR value of greater than or equal to 30% from baseline.

- **The onset of events of albuminuria progression/regression** is based on the ACR measurements quantified by a central laboratory. The date of the progression/regression event will be defined as the visit date of the first urine sample for the potential progression/regression findings.

Renal Composites

The components of the renal composite endpoints, such as requirement for renal replacement therapy and doubling of serum creatinine, identified by the investigators or the sponsor for meeting the criteria prespecified in the charter will be sent to the independent Endpoint Adjudication Committee (EAC).

Requirement for Renal Replacement Therapy

In the absence of universally accepted guidelines that define the onset of end-stage kidney disease (ESKD), the following definitions have been developed to identify and adjudicate ESKD events.

1. Diagnosis

Worsening uremia in patients progressing from chronic kidney disease to ESKD causes characteristic symptoms that require renal replacement therapy in the form of dialysis or transplantation. The requirement of ongoing renal replacement therapy establishes the diagnosis of ESKD. In some cases, the diagnosis can be made in the absence of renal replacement therapy when certain criteria are fulfilled.

- Kidney transplantation
  Definitive renal replacement therapy prescribed when uremic symptoms have already occurred, or are anticipated to occur, due to the progression of irreversible chronic kidney disease. Death during the transplant surgery will be considered kidney transplantation.
- Chronic dialysis
  ESKD will be diagnosed if dialysis is performed for 30 days or more and is not subsequently known to recover. Indications for dialysis are indicated in section 2 below.
- Dialysis not administered
  In cases where dialysis is not available or not administered due to futility or subject refusal, the diagnosis of ESKD will require sustained eGFR of <15 ml/min/1.73 m^2 (by CKD-EPI formula and confirmed by repeat central laboratory measure).

2. Onset of ESKD

The mode of onset of ESKD will be adjudicated into the following categories:

- Chronic progression
- Acute deterioration, diagnosed when the decline in kidney function is sudden and acute kidney injury is superimposed on chronic kidney disease resulting in renal replacement therapy.

3. Confirmation of ESKD

- In cases where renal replacement therapy is given in the form of dialysis, the patient will be contacted at least 90 days after the initiation of dialysis to document whether dialysis is continuing.
- If the patient recovers renal function, (defined as patient taken off dialysis because the physician evaluates that patient has enough renal function to live independently) the diagnosis of ESKD will be rescinded.
- If the patient is known to have received dialysis for >30 days but <90 days, and not known to recover, ESKD will be confirmed. The reason for the unavailability of information beyond 30 days should be clearly documented by the investigator.

If dialysis was initiated, but not continued for 30 days due to death, futility of therapy, or transplantation, the patient will be considered to have reached ESKD. In this situation, the reason for discontinuation of dialysis should be clearly documented by the investigator.

- If dialysis is known to have been continued for <30 days and there is no further information available about the event, the adjudicators will use their discretion in considering the event as an endpoint.

4. Date of ESKD

- If an event is adjudicated as ESKD due to kidney transplantation, the date of the transplantation will be the date of the event if transplantation was the first form of renal replacement therapy given.
- If an event is adjudicated as ESKD due to initiation of dialysis, the date when dialysis was initiated will be the date of the event.
- In cases where dialysis is not available or not administered due to futility or subject refusal, the date of ESKD will be when eGFR falls below 15 ml/min/1.73 m^2, as determined by central or local laboratory measurements.

Information around presence or absence of symptoms of uremia will also be collected, if available, for subjects meeting the ESKD endpoint; however this will not affect the final adjudication decision which will be based on the primary definition of ESKD as described in sections 1-4 above.

- Symptomatic uremia
  Symptomatic uremia is diagnosed in the presence of the uremic syndrome, which is a constellation of signs and symptom involving several different systems, including:
  - General: Pruritus, dry skin, fatigue, anhedonia
  - Metabolic: Deterioration in nutritional status, recent significant weight loss, electrolyte or acid base disturbances (severe hyperkalemia or severe acidosis);
  - Gastrointestinal: Nausea, vomiting
  - Neurological: Neuropathy, encephalopathy, psychiatric disturbances, seizures;
  - Volume overload, including difficult-to-control or accelerated hypertension;
  - Bleeding diathesis not attributable to other causes;

    - Pleuritis or pericarditis of uremic origin or other
    - Severe hyperparathyroidism
- Advanced asymptomatic uremia
  The initiation of dialysis is generally performed when eGFR declines to <15 ml/min/1.73 m^2 on a subjective basis in anticipation of development of uremic symptoms. If no symptoms are documented for initiation of dialysis, asymptomatic uremia will be diagnosed. In the minority of patients who exhibit no symptoms even at very low eGFR values (such as <8 ml/min/1.73 m^2), but for whom renal replacement therapy is initiated in the view of benefits of therapy, the diagnosis will be of advanced asymptomatic uremia.

40% Reduction in eGFR

A 40% reduction in eGFR will be defined as a greater than or equal to 40% reduction in eGFR from the baseline assessment that persists for 30 days or more and is not thought to be due to reversible causes.

- The baseline eGFR will be used to compare subsequent values and determine if 40% reduction in eGFR has occurred.
- Both central eGFR values and local lab values, if available, may be used to calculate the change in eGFR.
- Cases in which there is a single observation or there are not 2 consecutive observations of 40% reduction in eGFR will not be submitted to the Renal EAC for adjudication.
- However, cases in which there is a single observation of 40% reduction in eGFR at the last measurement during the studies will be submitted to the Renal EAC for adjudication.
- If a confirmatory central lab value cannot be collected due to death or dialyses and there is no evidence of acute kidney injury, the event will be adjudicated positively.
- It is assumed that as a matter of good general clinical practice, the investigator will make reasonable attempts to exclude reversible causes such as volume depletion or nephrotoxic medication. The event will be adjudicated positively once the initial change has been confirmed at 30 days or more, and if the process is determined to be irreversible. The date of the event will be the date on which the change was first recorded.

F. Safety

Adverse events (AEs) will be coded using the latest version of the *Medical Dictionary for Regulatory Activities* (*MedDRA*) at the time of database lock.

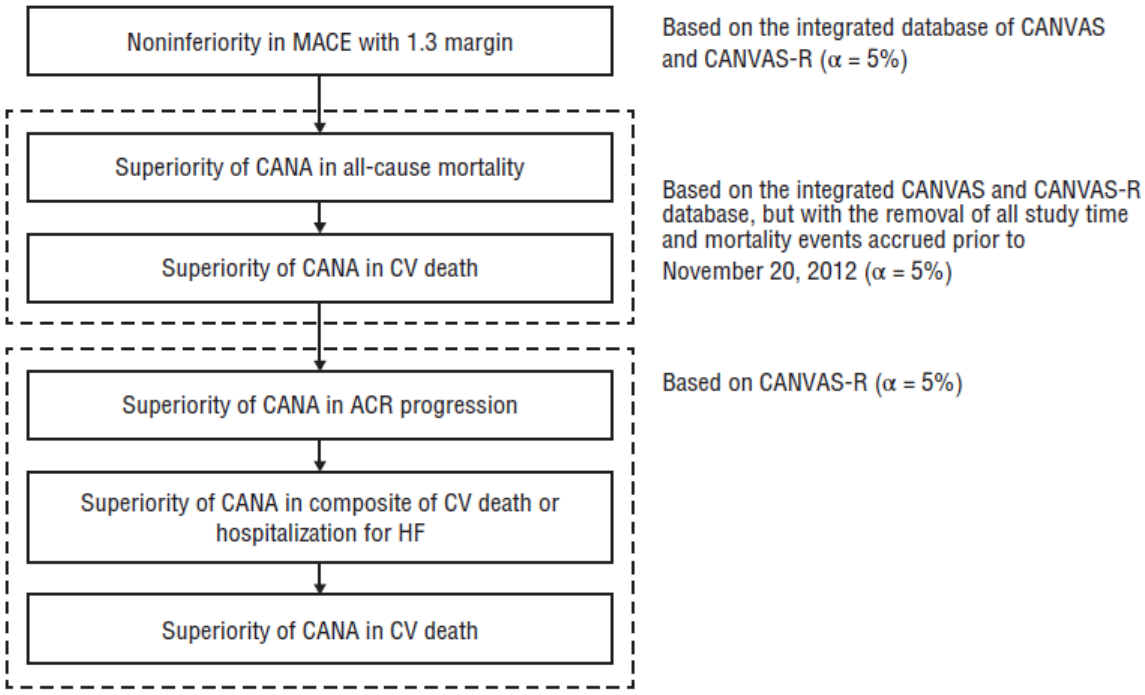
CANVAS-R was started after the approval of canagliflozin. Since the safety profile of canagliflozin had been well established in the Phase 3 program, the AE collection in CANVAS-R was streamlined to include:

- Serious AEs;
- AEs that resulted in study drug discontinuation; and
- All AEs (serious and nonserious) for selected AEs of interest.

After the approval of protocol amendment INT-6 (January 2014), the AE data collection in CANVAS was also streamlined in the same fashion as CANVAS-R.

AEs of interest include male genital mycotic infections, selected malignancies (bladder, renal cell, pheochromocytoma, Leydig cell tumors), photosensitivity, venous thromboembolism, bone fracture, amputation, and diabetic ketoacidosis. Hepatic toxicity, pancreatitis, and hypersensitivity were also of interest.

Figure S1. Prespecified hypothesis testing plan[1] and results



MACE, major adverse cardiovascular events; CANA, canagliflozin; CV, cardiovascular; HF, heart failure.
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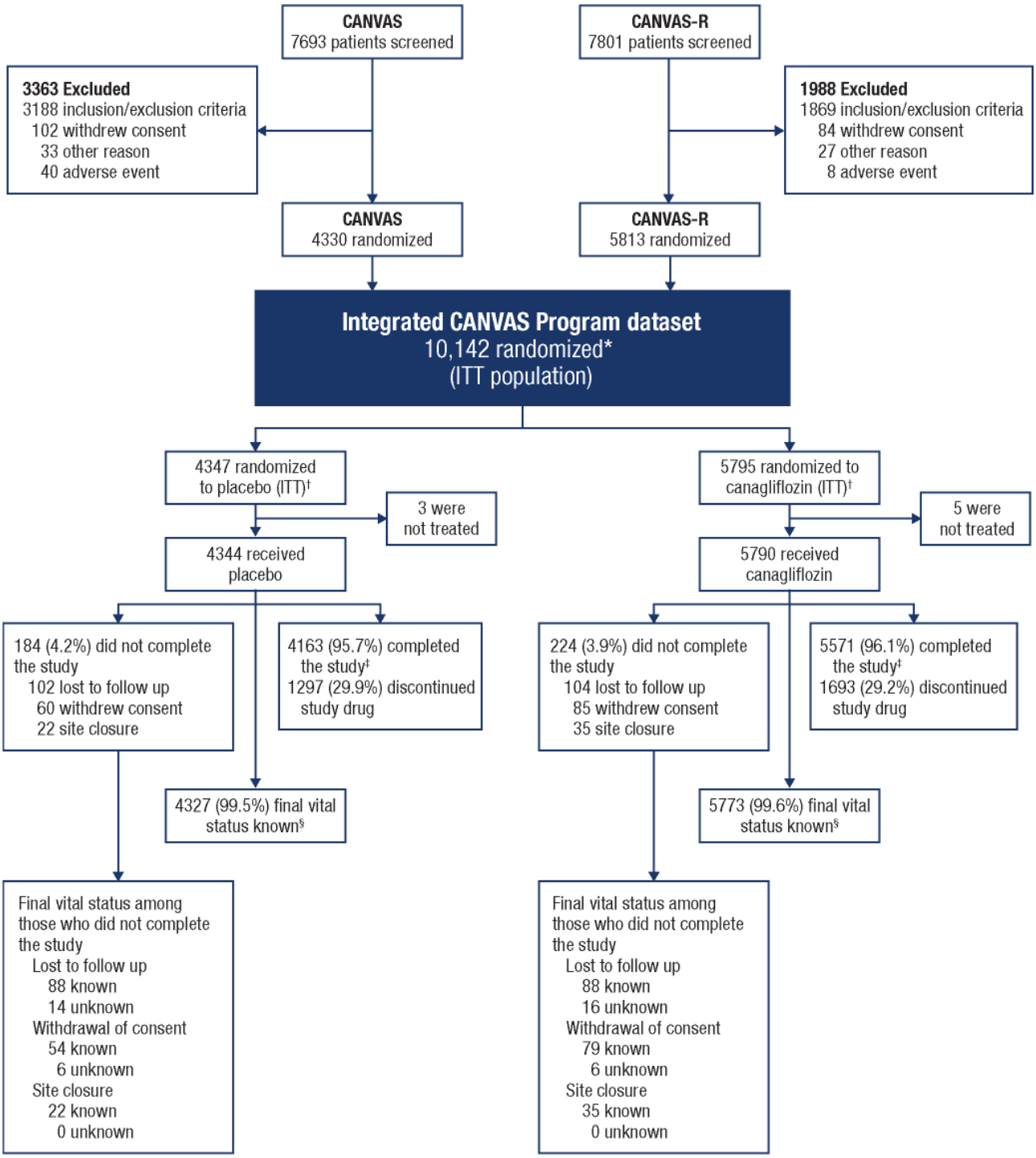
Hazard ratios, 95% CIs, and P values for the prespecified sequential hypothesis testing plan

	Canagliflozin Per 1000 patient-years	Placebo Per 1000 patient-years	Hazard ratio (95% confidence interval)	P value
Based on the integrated database of CANVAS and CANVAS-R				
Primary outcome	26.93	31.48	0.86 (0.75–0.97)	<0.0001* 0.0158†
Based on the integrated database of CANVAS and CANVAS-R, but with the removal of all study time and mortality events accrued prior to November 20, 2012				
All-cause mortality	19.05	20.12	0.90 (0.76–1.07)	0.2452
Cardiovascular death	12.82	12.74	0.96 (0.77–1.18)	NA
Based on CANVAS-R				
Albumin:creatinine ratio progression	99.80	153.01	0.64 (0.57–0.73)	NA
Cardiovascular death or hospitalization for heart failure	15.85	21.91	0.72 (0.55–0.94)	NA
Cardiovascular death	10.06	11.60	0.86 (0.61–1.22)	NA

*Noninferiority P value. †Superiority P value. NA=not applicable because prior P >0.05

Figure S2. Trial flow chart



ITT, intent-to-treat.

*One patient was randomized at 2 different sites and therefore the second randomized ID was excluded from the ITT analysis set.

† Percentages calculated based on the ITT analysis set.

‡ A patient is considered as having completed the study, regardless of whether the patient is on or off study drug, if the patient is followed until a time point between the notification of the trial end date (November 1, 2016) and the trial end date (February 23, 2017), or until the time of death for those who died prior to the trial end date.

§ Including results from the search of public records.

Figure S3. Discontinuation from randomized treatment in the CANVAS Program, CANVAS, and CANVAS-R

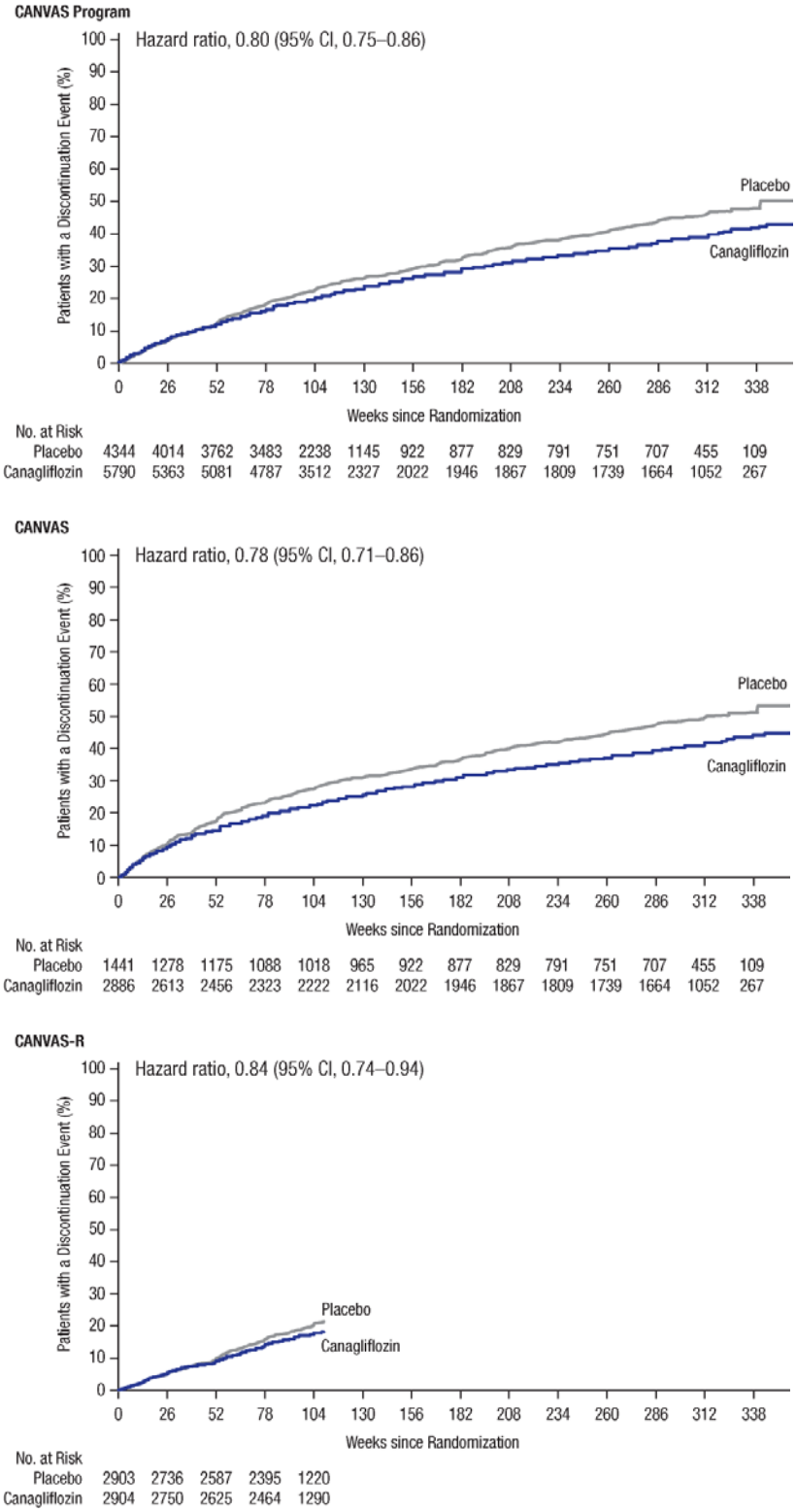
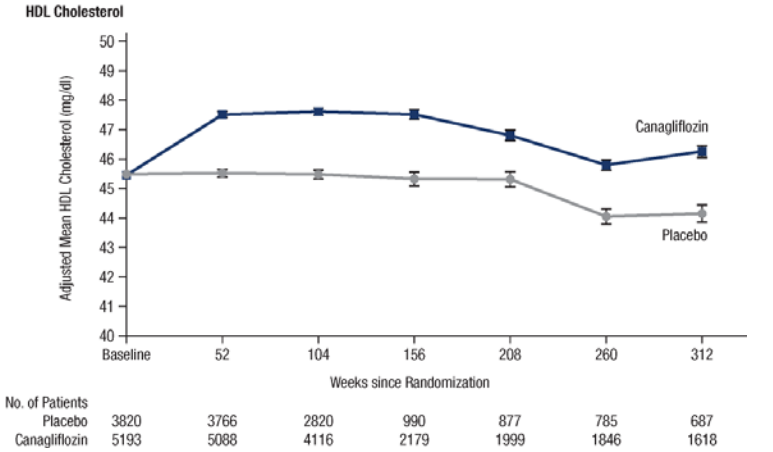
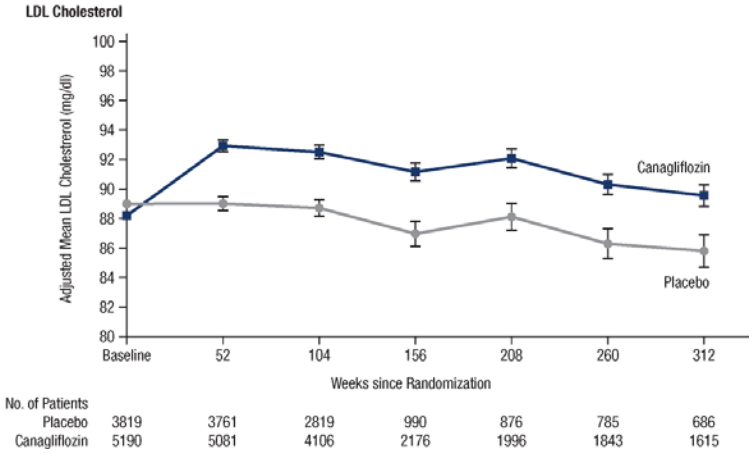


Figure S4. Effects of canagliflozin on high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, and LDL/HDL cholesterol ratio in the CANVAS Program





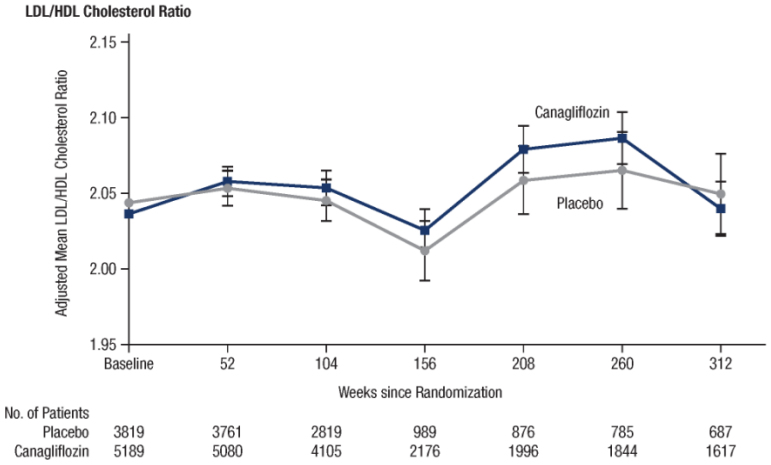


Figure S5. Highest-level atraumatic lower-limb amputations experienced by participants in the CANVAS Program

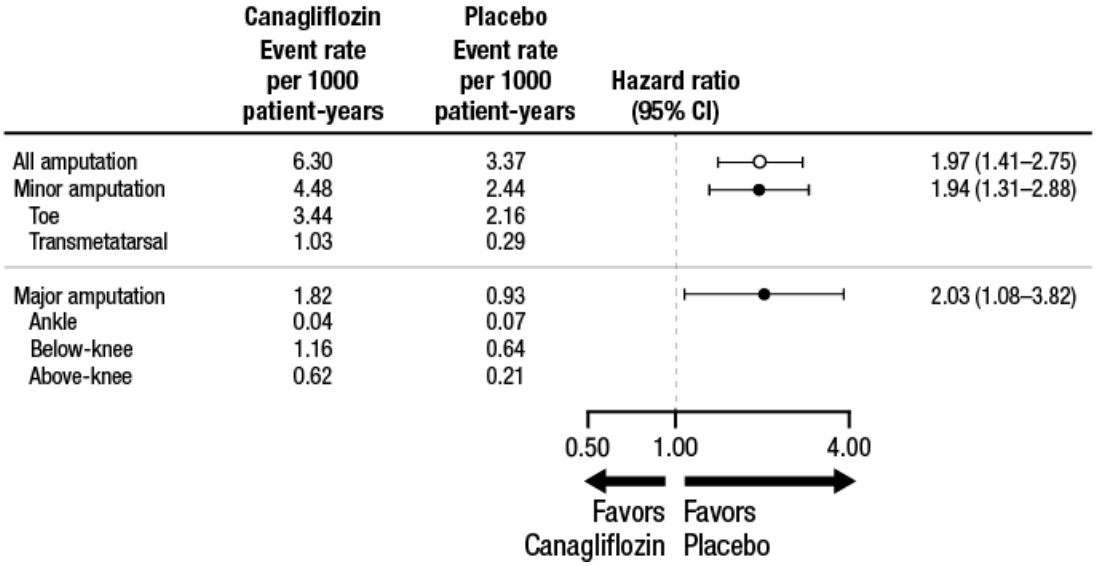


Table S1. CANVAS and CANVAS-R inclusion and exclusion criteria[2,3]

CANVAS	CANVAS-R
INCLUSION CRITERIA	
Man or woman with a diagnosis of type 2 diabetes with glycated hemoglobin level ≥7.0% to ≤10.5% at screening and be either (1) not currently on antihyperglycemic agent (AHA) therapy or (2) on AHA monotherapy or combination therapy with any approved class of agents: e.g., sulfonylurea, metformin, peroxisome proliferator-activated receptor gamma (PPARγ) agonist, alpha-glucosidase inhibitor, glucagon-like peptide-1 (GLP-1) analogue, dipeptidyl peptidase-4 (DPP-4) inhibitor, or insulin.	Same
History or high risk of cardiovascular disease defined on the basis of either: – Age ≥30 years with documented symptomatic atherosclerotic cardiovascular disease: including stroke; myocardial infarction (MI); hospital admission for unstable angina; coronary artery bypass graft (CABG); percutaneous coronary intervention (PCI; with or without stenting); peripheral revascularization (angioplasty or surgery); symptomatic with documented hemodynamically-significant carotid or peripheral vascular disease; or amputation secondary to vascular disease. – Age ≥50 years with 2 or more of the following risk factors determined at the screening visit: duration of type 2 diabetes of 10 years or more, systolic blood pressure >140 mmHg (average of 3 readings) recorded at the screening visit, while the subject is on at least one blood pressure–lowering treatment, current daily cigarette smoker, documented microalbuminuria or macroalbuminuria, or documented high-density lipoprotein (HDL) cholesterol of <1 mmol/l (<39 mg/dl).	Same
Women must be: – Postmenopausal, defined as >45 years of age with amenorrhea for at least 18 months, or >45 years of age with amenorrhea for at least 6 months and less than 18 months and a serum follicle stimulating hormone (FSH) level >40 IU/ml, or – Surgically sterile (have had a hysterectomy or bilateral oophorectomy, tubal ligation), or otherwise be incapable of pregnancy, or – Heterosexually active *and* practicing a highly effective method of birth control, including hormonal prescription oral contraceptives, contraceptive injections, contraceptive patch, intrauterine device, double-barrier method (e.g., condoms, diaphragm, or cervical cap with spermicidal foam, cream, or gel), or male partner sterilization, consistent with local regulations regarding use of birth control methods for subjects participating in clinical trials, for the duration of their participation in the study, or – Not heterosexually active. Note: subjects who are not heterosexually active at screening must agree to utilize a highly effective method of birth control if they become heterosexually active during their participation in the study.	Same
Women of childbearing potential must have a negative urine β-human chorionic gonadotropin (β-hCG) pregnancy test at screening and baseline (predose, Day 1).	Same
Willing and able to adhere to the prohibitions and restrictions specified in this protocol.	Same
Subjects must have signed an informed consent document indicating that they understand the purpose of and procedures required for the study and are willing to participate in the study.	
To participate in the optional pharmacogenomic component of this study, subjects must have signed the informed consent form for pharmacogenomic research indicating willingness to participate in the pharmacogenomic component of the study (where local regulations permit). Refusal to give consent for this component does not exclude a subject from participation in the clinical study.	N/A
Subjects must have taken ≥80% of their single-blind placebo capsules during the 2-week run-in period at Day 1 to be eligible for randomization.	Same
EXCLUSION CRITERIA	
History of diabetic ketoacidosis, type 1 diabetes, pancreas or beta-cell transplantation, or diabetes secondary to pancreatitis or pancreatectomy.	Same
On an AHA and not on a stable regimen (i.e., agents and doses) for at least 8 weeks before the screening visit and through the screening/run-in period. Note: a stable dose of insulin is defined as no change in the insulin regimen (i.e., type[s] of insulin) and ≤15% change in the total daily dose of insulin (averaged over 1 week to account for day-to-day variability).	N/A
Fasting fingerstick glucose at site >270 mg/dl (>15 mmol/l) at Baseline/Day 1 – For patients on a sulfonylurea agent or on insulin: fasting fingerstick glucose at site <110 mg/dl (<6 mmol/l) at Baseline/Day 1. Note: at the investigator's discretion, based upon an assessment of recent self-monitored blood glucose (SMBG) values, subjects meeting either of these fingerstick glucose exclusion criteria may continue the single-blind placebo and return to the investigational site within 14 days and may be randomized if the repeat fasting fingerstick value no longer meets the exclusion criterion. Subjects with fingerstick glucose >270 mg/dl (>15 mmol/l) may have their AHA regimen adjusted and be rescreened once on a stable regimen for at least 8	Not included

CANVAS	CANVAS-R
weeks.	
History of one or more severe hypoglycemic episode within 6 months before screening. Note: a severe hypoglycemic episode is defined as an event that requires the help of another person.	Same
History of hereditary glucose-galactose malabsorption or primary renal glucosuria.	Same
Ongoing, inadequately controlled thyroid disorder. Note: subjects on thyroid hormone-replacement therapy must be on a stable dose for at least 6 weeks before Day 1.	Same
Renal disease that required treatment with immunosuppressive therapy or a history of dialysis or renal transplant. Note: subjects with a history of treated childhood renal disease, without sequelae, may participate.	Same
MI, unstable angina, revascularization procedure, or cerebrovascular accident within 3 months before screening, or a planned revascularization procedure, or history of New York Heart Association (NYHA) Class IV cardiac disease.	same
Findings on 12-lead electrocardiogram (ECG) that would require urgent diagnostic evaluation or intervention (e.g., new clinically important arrhythmia or conduction disturbance).	Known ECG findings within 3 months before screening that would require urgent diagnostic evaluation or intervention (e.g., new clinically important arrhythmia or conduction disturbance).
History of hepatitis B surface antigen or hepatitis C antibody positive (unless associated with documented persistently stable/normal range aspartate aminotransferase [AST] and alanine aminotransferase [ALT] levels), or other clinically active liver disease.	Same
Any history of or planned bariatric surgery.	Same
Estimated glomerular filtration rate (eGFR) <30 ml/min/1.73 m^2 at screening (provided by the central laboratory) – For subjects taking metformin: at screening, serum creatinine ≥1.4 mg/dl (124 µmol/l) for men or ≥1.3 mg/dl (115 µmol/l) for women; no contraindication to the use of metformin (including eGFR) based on the label of the country of investigational site	eGFR <30 ml/min/1.73 m^2 at screening visit.
ALT levels >2.0 times the upper limit of normal (ULN) or total bilirubin >1.5 times the ULN at screening, unless in the opinion of the investigator and as agreed upon by the sponsor's medical officer, the findings are consistent with Gilbert's disease.	Same
History of malignancy within 5 years before screening (exceptions: squamous and basal cell carcinomas of the skin and carcinoma of the cervix in situ, or a malignancy that in the opinion of the investigator, with concurrence with the sponsor's medical monitor, is considered cured with minimal risk of recurrence).	Same
History of human immunodeficiency virus (HIV) antibody positive.	Same
Subject has a current clinically important hematological disorder (e.g., symptomatic anemia, proliferative bone marrow disorder, thrombocytopenia).	Same
Investigator's assessment that the subject's life expectancy is less than 1 year, or any condition that in the opinion of the investigator would make participation not in the best interest of the subject, or could prevent, limit, or confound the protocol-specified safety or efficacy assessments.	Same
Major surgery (i.e., requiring general anesthesia) within 3 months of the screening visit or any surgery planned during the subject's expected participation in the study (except minor surgery; i.e., outpatient surgery under local anesthesia).	Same
Any condition that, in the opinion of the investigator, would compromise the well-being of the subject or prevent the subject from meeting or performing study requirements.	Same
N/A	Prior or current participation in another canagliflozin study.
Current use of other sodium glucose co-transporter 2 (SGLT2) inhibitor.	Current or prior use of an SGLT2 inhibitor.
Known allergies, hypersensitivity, or intolerance to canagliflozin or its excipients.	Same
Current use of a corticosteroid medication or immunosuppressive agent, or likely to require treatment with a corticosteroid medication (for longer than 2 weeks in duration) or an immunosuppressive agent. Note: subjects using inhaled, intranasal, intra-articular, or topical corticosteroids, or corticosteroids in therapeutic replacement doses may participate.	Same
Received an active investigational drug (including vaccines) or used an investigational medical device within 3 months before Day 1/baseline or received at least one dose of canagliflozin in a prior study.	Same
History of drug or alcohol abuse within 3 years before screening.	Same
Pregnant or breastfeeding or planning to become pregnant or breastfeed during the study.	Same
Employees of the investigator or study center, with direct involvement in the proposed study or other studies under the direction of that investigator or study center, as well as family members of the employees or the investigator.	Same

Table S2. Participant follow-up and time on treatment in CANVAS and CANVAS-R

	CANVAS		CANVAS-R	
	Canagliflozin	**Placebo**	**Canagliflozin**	**Placebo**
Mean (SD) follow-up, weeks	298.6 (70.2)	290.4 (79.9)	108.2 (19.7)	107.7 (20.1)
Mean (SD) time on treatment, weeks	229.2 (119.5)	209.9 (123.9)	95.4 (29.4)	93.5 (30.1)

SD, standard deviation.

Table S3. Reasons for premature discontinuation of randomized treatment in CANVAS, CANVAS-R, and the CANVAS Program

	CANVAS		CANVAS-R		CANVAS Program	
Participants, n (%)*	**Canagliflozin (n = 2886)**	**Placebo (n = 1441)**	**Canagliflozin (n = 2904)**	**Placebo (n = 2903)**	**Canagliflozin (n = 5790)**	**Placebo (n = 4344)**
Any reason	1187 (41.1)	706 (49.0)	506 (17.4)	591 (20.4)	1693 (29.2)	1297 (29.9)
Withdrawn from study medication	467 (16.2)	342 (23.7)	163 (5.6)	264 (9.1)	630 (10.9)	606 (14.0)
Adverse event	371 (12.9)	136 (9.4)	188 (6.5)	165 (5.7)	559 (9.7)	301 (6.9)
Other reason	108 (3.7)	72 (5.0)	106 (3.7)	107 (3.7)	214 (3.7)	179 (4.1)
Physician decision	71 (2.5)	46 (3.2)	29 (1.0)	29 (1.0)	100 (1.7)	75 (1.7)
Withdrew consent	71 (2.5)	55 (3.8)	8 (0.3)	6 (0.2)	79 (1.4)	61 (1.4)
Noncompliance with study drug	51 (1.8)	32 (2.2)	9 (0.3)	13 (0.4)	60 (1.0)	45 (1.0)
Protocol violation	18 (0.6)	9 (0.6)	2 (0.1)	5 (0.2)	20 (0.3)	14 (0.3)
Lost to follow-up	19 (0.7)	8 (0.6)	0	0	19 (0.3)	8 (0.2)
eGFR withdrawal criteria	5 (0.2)	3 (0.2)	1 (<0.1)	1 (<0.1)	6 (0.1)	4 (0.1))
Study terminated by sponsor	5 (0.2)	3 (0.2)	0	0	5 (0.1)	3 (0.1)
Product quality complaint	1 (<0.1)	0	0	1 (<0.1)	1 (<0.1)	1 (<0.1)

*n based on patients dosed; there were 8 patients randomized who did not receive randomized treatment.

Table S4. Baseline Therapy in Active Versus Placebo Groups in the Integrated Trials Program

Patients, n (%)	Canagliflozin (n = 5795)	Placebo (n = 4347)	Total (N = 10,142)*
Antihyperglycemic agents			
Insulin	2890 (49.9)	2205 (50.7)	5095 (50.2)
Sulfonylurea	2528 (43.6)	1833 (42.2)	4361 (43.0)
Metformin	4447 (76.7)	3378 (77.7)	7825 (77.2)
GLP-1 receptor agonist	222 (3.8)	185 (4.3)	407 (4.0)
DPP-4 inhibitor	697 (12.0)	564 (13.0)	1261 (12.4)
Cardioprotective agents			
Statin	4329 (74.7)	3270 (75.2)	7599 (74.9)
Antithrombotic	4233 (73.0)	3233 (74.4)	7466 (73.6)
RAAS inhibitor	4645 (80.2)	3471 (79.8)	8116 (80.0)
Beta blocker	3039 (52.4)	2382 (54.8)	5421 (53.5)
Diuretic	2536 (43.8)	1954 (45.0)	4490 (44.3)

GLP-1, glucagon-like peptide-1; DPP-4, dipeptidyl peptidase-4; RAAS, renin angiotensin aldosterone system.

*One participant was randomized at 2 different sites and only the first randomization is included in the ITT analysis set.

Table S5. Baseline characteristics for CANVAS, CANVAS-R, and the CANVAS Program

	CANVAS (n = 4330)	CANVAS-R (n = 5812)*	CANVAS Program (N = 10,142)*
Age, years, mean (SD)	62.4 (8.0)	64.0 (8.4)	63.3 (8.3)
Female, n (%)	1469 (33.9)	2164 (37.2)	3633 (35.8)
Race, n (%)			
White	3179 (73.4)	4765 (82.0)	7944 (78.3)
Asian	795 (18.4)	489 (8.4)	1284 (12.7)
Black or African American	105 (2.4)	231 (4.0)	336 (3.3)
Other†	251 (5.8)	327 (5.6)	578 (5.7)
Current smoker, n (%)	776 (17.9)	1030 (17.7)	1806 (17.8)
History of hypertension, n (%)	3795 (87.6)	5330 (91.7)	9125 (90.0)
History of heart failure, n (%)	515 (11.9)	946 (16.3)	1461 (14.4)
Duration of diabetes, years, mean (SD)	13.4 (7.5)	13.7 (7.9)	13.5 (7.8)
Drug therapy, n (%)			
Insulin	2174 (50.2)	2921 (50.3)	5095 (50.2)
Sulfonylurea	2033 (47.0)	2328 (40.1)	4361 (43.0)
Metformin	3171 (73.2)	4654 (80.1)	7825 (77.2)
GLP-1 receptor agonist	96 (2.2)	311 (5.4)	407 (4.0)
DPP-4 inhibitor	317 (7.3)	944 (16.2)	1261 (12.4)
Statin	3130 (72.3)	4469 (76.9)	7599 (74.9)
Antithrombotic	3099 (71.6)	4367 (75.1)	7466 (73.6)
RAAS inhibitor	3490 (80.6)	4626 (79.6)	8116 (80.0)
Beta blocker	2179 (50.3)	3242 (55.8)	5421 (53.5)
Diuretic	1901 (43.9)	2589 (44.5)	4490 (44.3)
Microvascular disease history, n (%)			
Retinopathy	865 (20.0)	1264 (21.7)	2129 (21.0)
Nephropathy	660 (15.2)	1114 (19.2)	1774 (17.5)
Neuropathy	1346 (31.1)	1764 (30.4)	3110 (30.7)
Atherosclerotic vascular disease history, n (%)‡			
Coronary	2375 (54.8)	3346 (57.6)	5721 (56.4)
Cerebrovascular	707 (16.3)	1251 (21.5)	1958 (19.3)
Peripheral	687 (15.9)	1426 (24.5)	2113 (20.8)
Any	2893 (66.8)	4431 (76.2)	7324 (72.2)
Cardiovascular disease history, n (%)§	2549 (58.9)	4107 (70.7)	6656 (65.6)
History of amputation, n (%)	78 (1.8)	160 (2.8)	238 (2.3)
Body mass index, kg/m^2, mean (SD)	32.1 (6.2)	31.9 (5.7)	32.0 (5.9)
Systolic BP, mmHg, mean (SD)	136.3 (15.7)	136.9 (15.8)	136.6 (15.8)
Diastolic BP, mmHg, mean (SD)	77.8 (9.7)	77.6 (9.6)	77.7 (9.7)
Glycated hemoglobin, %, mean (SD)	8.2 (0.9)	8.3 (1.0)	8.2 (0.9)
Total cholesterol, mmol/l, mean (SD)	4.4 (1.2)	4.4 (1.2)	4.4 (1.2)
Triglycerides, mmol/l, mean (SD)	2.0 (1.4)	2.1 (1.5)	2.0 (1.4)
HDL cholesterol, mmol/l, mean (SD)	1.2 (0.3)	1.2 (0.3)	1.2 (0.3)
LDL cholesterol, mmol/l, mean (SD)	2.3 (0.9)	2.3 (0.9)	2.3 (0.9)
LDL/HDL cholesterol ratio, mean (SD)	2.0 (0.9)	2.1 (0.9)	2.0 (0.9)
eGFR, ml/min/1.73 m², mean (SD)‖	77.2 (18.9)	75.9 (21.7)	76.5 (20.5)
Albumin:creatinine ratio, mg/g, median (interquartile range)¶	11.9 (6.6–36.4)	12.6 (6.7–46.7)	12.3 (6.7–42.1)
Normoalbuminuria, n (%)	3091 (71.7)	3916 (68.4)	7007 (69.8)
Microalbuminuria, n (%)	968 (22.5)	1298 (22.7)	2266 (22.6)
Macroalbuminuria, n (%)	250 (5.8)	510 (8.9)	760 (7.6)

SD, standard deviation; GLP-1, glucagon-like peptide-1; DPP-4, dipeptidyl peptidase-4; RAAS, renin angiotensin aldosterone system; BP, blood pressure; HDL, high-density lipoprotein; LDL, low-density lipoprotein; eGFR, estimated glomerular filtration rate. *One participant was randomized at 2 different sites and only the first randomization is included in the ITT analysis set. †Includes American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, multiple, other, and unknown. ‡Some participants had ≥1 type of atherosclerotic disease. §As defined in the protocol. ‖Values for eGFR categories calculated based on N of 4328 for CANVAS, 5812 for CANVAS-R, and 10,140 for the CANVAS Program. ¶Values for albuminuria categories calculated based on N of 4309 for CANVAS, 5724 for CANVAS-R, and 10,033 for the CANVAS Program.

Table S6. Effects of canagliflozin versus placebo on cardiovascular outcomes and death in CANVAS, CANVAS-R, and the CANVAS Program

	Number of events	Canagliflozin Per 1000 patient-years	Placebo Per 1000 patient-years	Hazard ratio (95% confidence interval)	P value[‡]
Cardiovascular mortality, nonfatal myocardial infarction, or nonfatal stroke					
CANVAS	658	26.89	30.36	0.88 (0.75–1.03)	
CANVAS-R	353	27.05	32.95	0.82 (0.66–1.01)	
CANVAS Program	1011	26.93	31.48	0.86 (0.75–0.97)	0.5980
Total mortality					
CANVAS	476	17.67	20.89	0.84 (0.70–1.01)	
CANVAS-R	205	16.32	17.57	0.92 (0.70–1.21)	
CANVAS Program	681	17.31	19.50	0.87 (0.74–1.01)	0.5675
Cardiovascular mortality					
CANVAS	322	12.15	13.73	0.88 (0.70–1.10)	
CANVAS-R	131	10.06	11.60	0.86 (0.61–1.22)	
CANVAS Program	453	11.60	12.84	0.87 (0.72–1.06)	0.9387
Cardiovascular mortality or hospitalization for heart failure					
CANVAS	427	16.42	19.94	0.82 (0.67–0.99)	
CANVAS-R	225	15.85	21.91	0.72 (0.55–0.94)	
CANVAS Program	652	16.27	20.78	0.78 (0.67–0.91)	0.4584
Nonfatal myocardial infarction					
CANVAS	238	9.44	11.06	0.85 (0.65–1.11)	
CANVAS-R	136	10.55	12.34	0.85 (0.61–1.19)	
CANVAS Program	374	9.74	11.61	0.85 (0.69–1.05)	0.9777
Nonfatal stroke					
CANVAS	159	6.54	6.72	0.97 (0.70–1.35)	
CANVAS-R	115	8.71	10.62	0.82 (0.57–1.18)	
CANVAS Program	274	7.12	8.39	0.90 (0.71–1.15)	0.4978
Hospitalization for heart failure					
CANVAS	138	5.19	6.71	0.77 (0.55–1.08)	
CANVAS-R	105	6.34	11.29	0.56 (0.38–0.83)	
CANVAS Program	243	5.50	8.68	0.67 (0.52–0.87)	0.2359

[‡]P value for homogeneity between CANVAS and CANVAS-R.

Table S7. Effects of canagliflozin versus placebo on renal outcomes in CANVAS, CANVAS-R, and the CANVAS Program

	Number of events	Canagliflozin Per 1000 patient-years	Placebo Per 1000 patient-years	Hazard ratio (95% confidence interval)	P value*
Progression of albuminuria					
CANVAS	1374	84.96	106.32	0.80 (0.72–0.90)	
CANVAS-R	1081	99.80	153.01	0.64 (0.57–0.73)	
CANVAS Program	2455	89.38	128.71	0.73 (0.67–0.79)	0.0184
					0.8750[†]
Regression of albuminuria					
CANVAS	596	233.87	147.40	1.56 (1.30–1.87)	
CANVAS-R	734	388.69	221.96	1.80 (1.55–2.09)	
CANVAS Program	1330	293.43	187.45	1.70 (1.51–1.91)	0.4587
40% reduction in eGFR,[‡] RRT, or renal death[§]					
CANVAS	169	5.55	9.91	0.56 (0.41–0.75)	
CANVAS-R	80	5.50	7.87	0.71 (0.45–1.11)	
CANVAS Program	249	5.54	9.03	0.60 (0.47–0.77)	0.3868

*P value for homogeneity between CANVAS and CANVAS-R.

[†]Gail-Simon P value.

[‡]40% reductions of eGFR were required to be sustained, defined as being present on at least 2 consecutive measurements more than 30 days apart, and were adjudicated by an expert committee

[§]RRT- Need for RRT due to end-stage kidney disease defined as a need for dialysis or transplantation for at least 30 days, and adjudicated by an expert committee. Renal death defined as death where the proximate cause was renal as defined by the Endpoint Adjudication Committee. There were only 3 renal deaths (all in the placebo group).

Table S8. Effects of canagliflozin versus placebo on atraumatic lower limb amputation in key subgroups in the CANVAS Program

	Canagliflozin Per 1000 patient-years	Placebo Per 1000 patient-years	Hazard ratio (95% confidence interval)
History of amputation			
Yes	96.30	59.16	2.15 (1.11–4.19)
No	4.68	2.48	1.88 (1.27–2.78)
History of peripheral vascular disease			
Yes	12.09	8.16	1.39 (0.80–2.40)
No	5.20	2.41	2.34 (1.53–3.58)

Table S9. Effects of canagliflozin versus placebo on fracture in CANVAS, CANVAS-R, and the CANVAS Program

	Canagliflozin Per 1000 patient-years	Placebo Per 1000 patient-years	Hazard ratio (95% confidence interval)	P value*
Low-trauma fracture (primary outcome)				
CANVAS	12.98	8.31	1.56 (1.18–2.06)	
CANVAS-R	7.87	10.30	0.76 (0.52–1.12)	
CANVAS Program	11.58	9.17	1.23 (0.99–1.52)	0.003
All fracture (secondary outcome)				
CANVAS	16.92	10.94	1.55 (1.21–1.97)	
CANVAS-R	11.42	13.23	0.86 (0.62–1.19)	
CANVAS Program	15.40	11.93	1.26 (1.04–1.52)	0.005

Analysis of fractures included all events at any time point in all patients who were randomized and received ≥1 dose of study drug.

*P value for homogeneity between CANVAS and CANVAS-R.

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