

Supplemental Online Content

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eFigure 1. Kaplan-Meier Curves for Primary Endpoint MACE in patients with and without established CVD

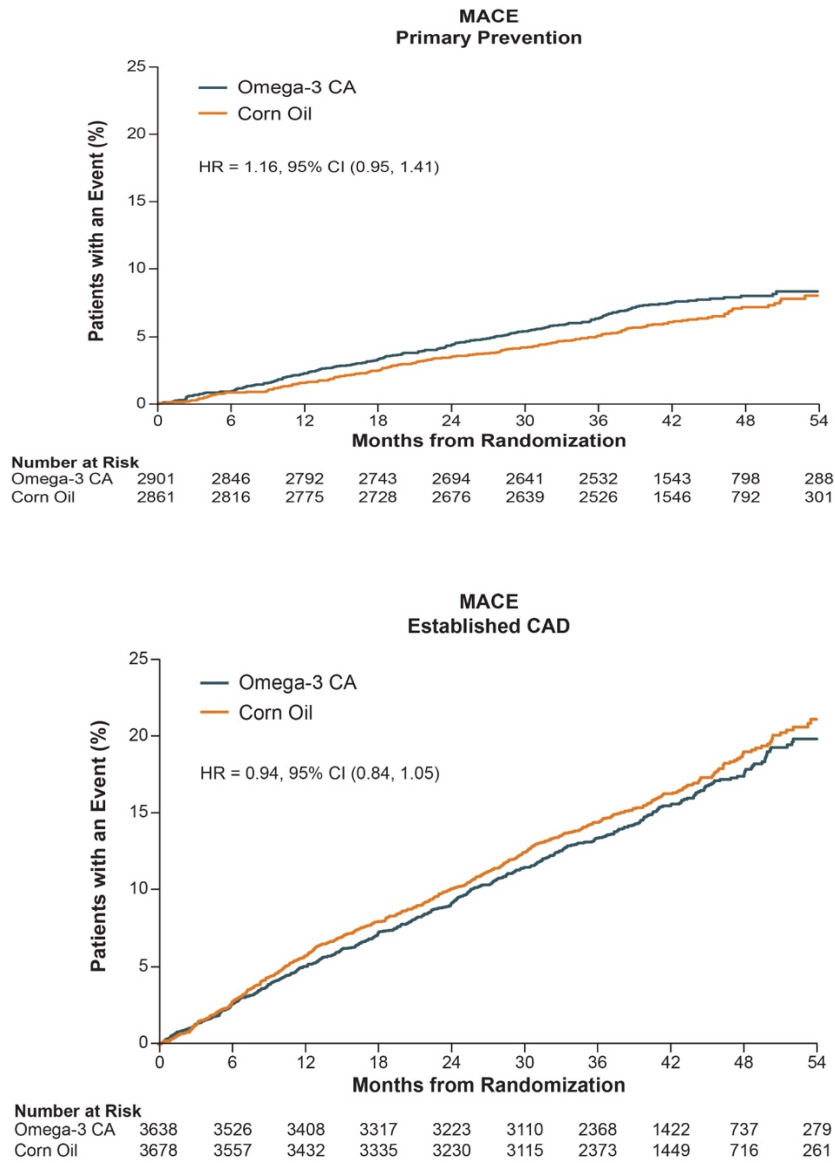
eFigure 2. Kaplan-Meier Curves for Investigator Reported Atrial Fibrillation

eMethods.

Listing of All Committees, DSMB, and Investigators.

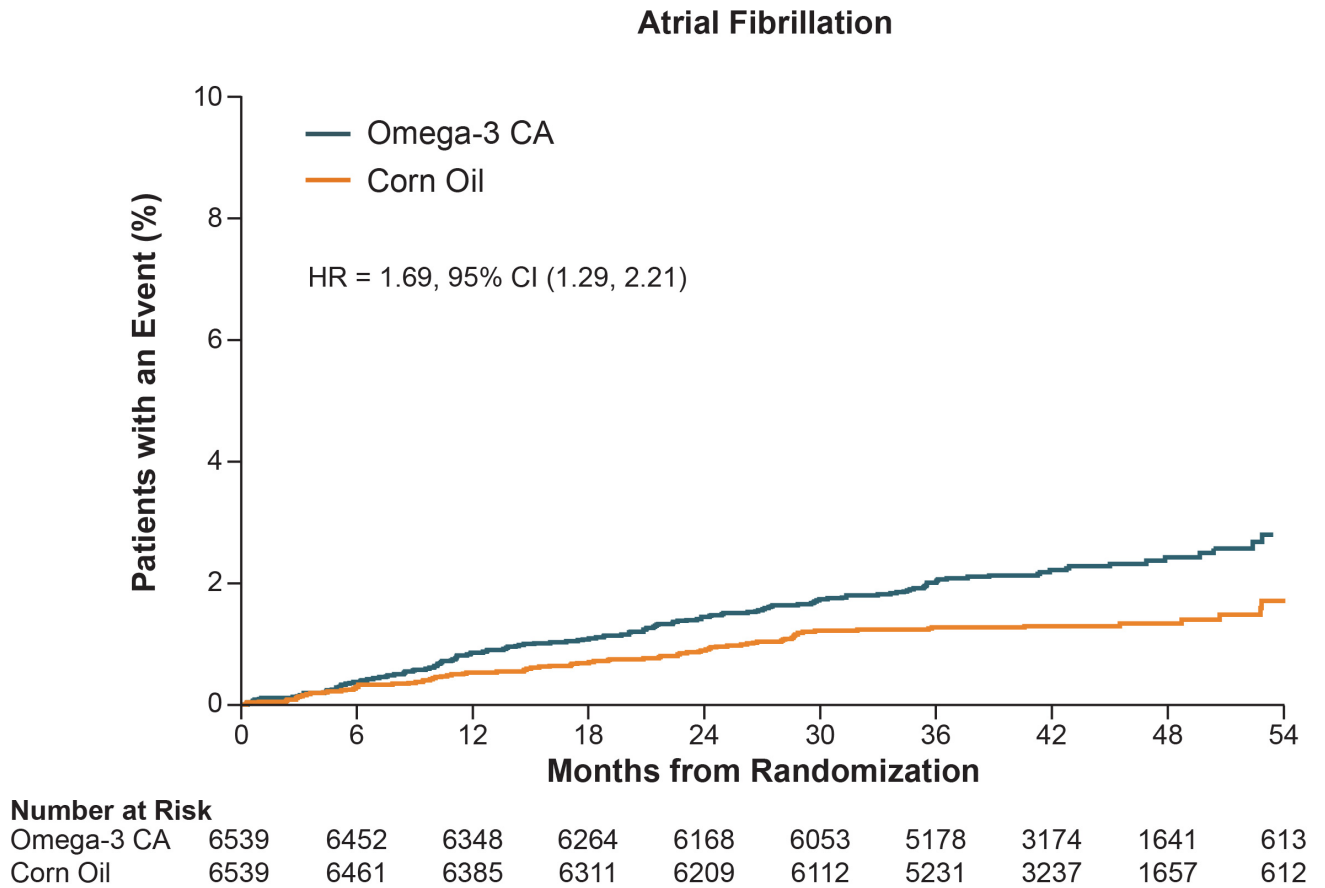
This supplemental material has been provided by the authors to give readers additional information about their work.

eFigure 1. Kaplan-Meier Curves for Primary Endpoint MACE in patients with and without established CVD



Kaplan-Meier curves illustrating the time to first incidence of any component of the primary composite endpoint of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, coronary revascularization and hospitalization for unstable angina in patients without (upper) or with (lower) clinically established cardiovascular disease at baseline, treated with corn oil or omega-3 CA.

eFigure 2. Kaplan-Meier Curves for Investigator Reported Atrial Fibrillation



Kaplan-Meier curves illustrating the time to first incidence of investigator reported atrial fibrillation.

eMethods.

Censoring rules for all outcome measures and vital status

For the analysis of the primary and all key secondary endpoints, except for the analyses of time to cardiovascular death and time to all-cause death, patients will be censored at the earliest of withdrawal of consent date and last study contact. Complete endpoint information will be pursued with every effort for all patients regardless of their study medication status, unless they exercise their right to withdraw consent. Patients who have a non-fatal event will continue study follow-up. Any event observed after the earliest of withdrawal of consent date and last study contact will not be included in the analysis. Last study contact is defined as the latest of the dates of assessments contributing to an opportunity to assess as to whether the patient has had every component of the endpoint being analyzed.

The dates of assessments that will be used include, but are not limited to,

- Date of randomization
- Start and end dates of dosing
- Date of collection of laboratory evaluations
- Date of vital sign testing
- Date of physical examinations
- Date of ECG
- Start and end dates of concomitant medications
- Start and end dates of hospitalization
- Start and end dates of AE
- Start and end dates of bleeding event
- Date of event (if not endpoint of interest)
- Date of telephone communication with patient or a designated third party on behalf of the patient, such as hospital or immediate family
- Date of end of treatment visit or early termination visit
- Date of consent withdrawn
- Date of death (if not endpoint of interest and if not reported on vital status form only)

If the last contact date is partially missing or missing, this partially missing or missing date will be imputed to the earliest possible date. The imputed last contact date should not be earlier than any of the dates considered in the derivation of the last contact. Because data on vital status (dead or alive) is consistently pursued for all patients, including those potentially lost to follow up or withdrawn from the study, the analysis of time to all-cause death will utilize data which extends even beyond last study contact and withdrawal of consent date. For the analysis of time to all-cause death, patients who have not had the event in question will be censored at the latest of the date of last study contact and last date known to be alive.

All deaths, including those recorded at the time of vital status assessment, will be adjudicated. Because undetermined deaths will be assumed to be cardiovascular, the analysis of time to cardiovascular death as a single outcome measure will utilize data which extends beyond last study contact and withdrawal of consent date. For the analysis of time to cardiovascular death, patients

will be censored at the latest of the date of last study contact, last date known to be alive, and date of non-cardiovascular death.

Imputation rules and missing data

For deaths with a missing or partially missing date the following rules apply.

- If only the day part of the death date is missing and occurs in the same month and year as the date of last contact, the date of last contact will be used as the death date. Otherwise, the first day of the month will be used to complete the death date.
- If the day and month parts of the death date are missing and occur in the same year as the date of last contact, the date of last contact will be used as the death date. Otherwise, January 1 will be used to complete the death date.
- If the death date is completely missing, the date of last contact will be used as the death date.

For all other efficacy events (i.e. myocardial infarction, stroke, emergent/elective coronary revascularization, hospitalization for unstable angina, atrial fibrillation, heart failure) with a missing or partially missing date of onset the following rules apply.

- If only the day part of the onset date is missing and occurs in the same month and year as the date of randomization, the date of randomization will be used as the onset date. Otherwise, the first day of the month will be used to complete the onset date.
- If the day and month parts of the onset date are missing and occur in the same year as the date of randomization, the date of randomization will be used as the onset date. Otherwise, January 1 will be used to complete the onset date.
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Author Contributions: Drs. Nicholls, Lincoff and Nissen had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Study Concept and Design: Drs. Nicholls, Nissen, Lincoff and Dianna Bash

Analysis and Interpretation of Data:

Stephen J Nicholls MBBS PhD*¹, A Michael Lincoff MD*², Michelle Garcia RN BSN CCRC², Dianna Bash BSN², Christie M Ballantyne MD³, Philip J Barter MBBS PhD⁴, Michael H. Davidson MD⁵, John J.P. Kastelein MD PhD⁶, Wolfgang Koenig MD⁷, Darren K. McGuire MD MHSc⁸, Dariush Mozaffarian PhD⁹, Terje R Pedersen MD¹⁰, Paul M Ridker MD¹¹, Kausik Ray MBBS DPhil¹², Brian G Katona PharmD¹³, Anders Himmelmann MD PhD¹⁴, Larrye E Loss PharmD MBA¹³, Martin Rensfeldt¹⁴, Torbjörn Lundström MD PhD¹⁴, Rahul Agrawal MD¹⁴, Venu Menon MD², Kathy Wolski MPH² and Steven E Nissen MD².

Drafting of the Manuscript:

Stephen J Nicholls MBBS PhD*¹, A Michael Lincoff MD

*Drs. Nicholls and Lincoff contributed equally to this article

Corresponding Author: Steven E. Nissen MD

Statistical Analysis:

For the purpose of the academic interpretation of the study, Kathy Wolski and Danielle Brennan performed all primary statistical analyses of the study that were used for the manuscript. Danielle Brennan and Kathy Wolski are both employees of the Cleveland Clinic Coordinating Center for Clinical Research.

Administrative, Technical, or Material Support: Dianna Bash and Michelle Garcia

Study Supervision: Drs. Nicholls, Lincoff, Nissen, Dianna Bash and Michelle Garcia

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Role of the Sponsor:

The sponsor, AstraZeneca Inc., participated actively in designing the study in collaboration with the steering committee, developing the protocol which was written by the steering committee, and provided logistical support during the trial, in terms of site management in collaboration with C5Research. The sponsor maintained the trial database. After completion of the trial, as specified in the study contract, a complete copy of the database was transferred to the Cleveland Clinic Coordinating Center for Clinical Research, where statistical analyses were performed by an independent statistician, Kathy Wolski, MPH. The results reported in the manuscript are the results of the analyses performed by Kathy Wolski. Stephen Nicholls and A Michael Lincoff wrote the manuscript and are responsible for the accuracy and completeness of the data and the analyses. While the steering committee and coordinating center had confidentiality agreements with the sponsor, the study contract specified that a copy of the study database be provided to C5Research for independent analysis. While employees of the sponsor are co-authors of the manuscript, they provided review of the drafts. The academic authors had unrestricted rights to publish the results. The manuscript was modified after consultation with co-authors. The final decision on content was exclusively retained by the academic authors.

Listing of All Committees, DSMB, and Investigators

Acknowledgements

Cleveland Clinic Coordinating Center for Clinical Research (C5Research):

Steven E. Nissen MD (Executive Committee Chairman), A. Michael Lincoff MD (Co-Principal Investigator), Stephen J. Nicholls MBBS PhD (Co-Principal Investigator)¹, Venu Menon MD (CEC Chairman), Vidysagar Kalahasti MD (CEC Associate Chairman), Kathy Wolski MPH (Lead Statistician), Danielle Brennan (Statistician), Dianna Bash RN (Lead Project Manager), Michelle Garcia RN BSN (Lead Project Manager), Jackie McCluskey RN (Project Manager), Kim Brown (CEC Manager), Diane Fabec (CEC Lead Project Manager), and Patty D'Angelo (CEC Project Manager).

¹Current affiliation: MonashHeart, Monash Health at Monash Medical Centre, Clayton, Australia.

ASTRAZENECA Inc :

Stefan Carlson, Jeyganesh Chandra, Jersey Chen, Lynne Durborow, Eva Jensen, Jesper Jensen, Mohamed Jessa, Björn Karlson, Justyna Łukaszewicz, Jie Mei, Per Nystrom, Matt Poole, Malin Söderbergh, Barry Traxler, Sally Walsh, and Asa Westin.

Executive Committee:

Steven E. Nissen MD (Chairman), Christie M. Ballantyne MD, Philip J. Barter MBBS PhD, Michael H. Davidson MD, John J.P. Kastelein MD PhD, Wolfgang Koenig MD, A. Michael Lincoff MD, Darren K. McGuire MD MHSc, Dariush Mozaffarian PhD, Stephen J. Nicholls MBBS PhD, Terje R. Pedersen MD, Kausik Ray MBBS DPhil, Paul M. Ridker MD, Brian G. Katona PharmD, and Anders Himmelmann MD PhD.

Steering Committee:

Phil Aylward, MA (Oxon) BM, BCh, PhD, FRCP,FRACP, FACC (Australia), Stefan P. Janssens MD, PhD (Belgium), Lawrence A. Leiter MD, FRCPC, FACP, FAHA (Canada), Shui-ping Zhao MD, PhD (China), Hong Chen MD (China), Miroslav Solar MD (Czech Republic), Børge G. Nordestgaard MD, DMSc (Denmark), Rein Kolk MD, PhD, FESC (Estonia), Róbert Gabor Kiss MD (Hungary), Alberico L. Catapano (Italy), Koutaro Yokote MD, PhD (Japan), Rimvydas Šlapikas MD (Lithuania), Francisco Padilla MD (Mexico), Ton Oude Ophuis MD PhD (Netherlands), Harvey White MB, ChB, DSc, FRACP, FACC, FESC, FAHA, FHKCC (Hon), FCSANZ, FRSNZ (New Zealand), Jarosław Jurowiecki MD (Poland), Andrey V. Susekov MD, PhD.D.Sc (Russia), Dirk Blom MBChB, PhD (South Africa), Seung-Hwan Han MD, PhD (Republic of Korea), Chern-En Chiang MD, PhD, FACC, FESC (Taiwan), Aleskander Parkhomenko MD, PhD (Ukraine), Kausik Ray BSc, MBChB, MD, FRCP, MPhil, FACC, FESC, FAHA (United Kingdom), Jarrett Berry MD (United States), Vera Bittner MD (United States), William Boden MD, FACC (United States), Alan S. Brown MD, FACC, FAHA, FNLA (United States), F. David Fortuin Jr. MD (United States), Robert Rosenson MD (United States), and Scott Wright MD (United States).

Data and Safety Monitoring Board:

Marc Pfeffer MD, PhD (Chairman), Kenneth W. Mahaffey MD., Stuart Pocock PhD, Jean L. Rouleau MD, Frank Sacks MD, and Brian Claggett PhD (non-voting observer).

Statistics Collaborative, Inc. Heidi Christ-Schmidt (Reporting statistician), Lijuan Zeng, (Independent programmer), and Janet Wittes (President of the reporting statistical group or Senior advisor).

Clinical Events Committee:

Venu Menon MD (CEC Chairman), Vidysagar Kalahasti MD (CEC Associate Chairman), CEC Adjudicators: Kenneth Uchino MD, Nirav Vora MD, Grant Reed MD, Paul Cremer MD, Erich Kiehl MD, Daniel Shivapour MD, Nael Hawwa MD, Brett Sperry MD, Rony Lahoud MD, Jayendrakumar Patel MD, Ann Gage MD, James Gentry MD, Rayji Tsutsui MD, Kyle Mandsager MD, Richard (Dane) Meredith MD, Aldo Schenone MD, Nyal Borges MD, Johnathan Hansen MD, Jeffrey Hedley MD, Bryan Wilner MD, Kara Denby MD, Amit Goyal MD, Robert Montgomery MD, Johnathan Hansen MD, Kim Brown (CEC Manager), Diane Fabec (Lead PM), and Patty D'Angelo (PM).

Statistical Programming Support: Craig Balog provided statistical support.

The South Australian Health and Medical Research Institute (SAHMRI): Liddy Griffith and Helen Loudis.

IQVIA:

Christine Hughes (Global Project Lead), Erin Wuerdeman (Global Project Lead), Anna Horabik (Global Medical Advisor), Jose Ferrari (Medical Advisor), Swati Ranade (Medical Advisor), Scott O'Neill (Project Lead), Degmo Gigot (Project Lead – EMEA), Daniela Garavaglia (Biostatistical Lead), Manshi Sangoi (Data Team Lead), Sandhya Korde (Data Team Lead), Alejandro Lead (Global Lab Lead), Jennifer Roush (CEVA Team Lead), Marites Rafanan (Global Clinical Lead), Wendy Lofton (Global Pharmacovigilance Lead), Saori Kano (Clinical Lead – Japan), Madalina Puscas Clinical Lead-EMEA), Agata Dabrowska (Clinical Lead-EMEA), Stephanie Mura (Clinical Lead-EMEA), Elena Milcic (Clinical Lead-EMEA), Lital Diaman (Clinical Lead-EMEA), Tara Ingram (Clinical Lead – Asia), Amanda Holman (Clinical Lead – Asia), Louis DiCave (Clinical Lead - North America), Lori Thurnauer (Clinical Lead -North America), and Linda Amstutz (Clinical Lead -USA/Mexico).

Investigators:

Australia, Christopher Argent (Paratus Clinical Research, Western Sydney), Mark Arya (Australian Clinical Research Network), David Colquhoun (Core Research Group), David Cross (Heart Care Partners Pty Ltd.), Peter Davidson (Cowra Medical Associates), Christopher Gilfillan (Box Hill Hospital), Laurence Howes (Gold Coast University Hospital), Karam Kostner (Dr Heart Pty Ltd), Peter Purnell (Cardiovascular Trials Western Australia), Neale Somes (Forbes Medical Centre), James Wolstenholme (Mingara Medical Centre), Matthew Worthley (Royal Adelaide Hospital), **Belgium**, Ian Buyschaert (Algemeen Stedelijk Ziekenhuis), Etienne Hoffer (C. H. R. de la Citadelle), Stefan Janssens (UZ Leuven), Jean Renkin (Cliniques Universitaires Saint-Luc), Harry Striekwold (Heilig Hart Ziekenhuis), Philippe van de Borne (Cliniques Universitaires de Bruxelles Hopital Erasme), Yves Vandekerckhove (AZ Sint-Jan), Guy Vereecken (Vereecken Guy), Mathias

Vrolix (Z.O.L - Campus St. Jan), Bart Wollaert (ZNA), **Canada**, Hani Alasaad (LMC Clinical Research Inc. (Barrie)), Ronnie Aronson (LMC Clinical Research Inc. (Bayview)), Alan Bell (Keele Medical Place), Guy Chouinard (Recherche Clinique Sigma Inc.), Richard Dumas (Centre de Recherche Clinique de Laval), Gilbert Gagne (LMC Clinical Research dba Manna Research Inc. Mirabel), Ginette Girard (DIEX Recherche Sherbrooke Inc.), Ronald Goldenberg (LMC Clinical Research Inc. (Thornhill)), Anil Gupta (Dr. Anil K. Gupta Medicine Professional Corporation), Milan Gupta (Brampton Research Associates), Michael Hartleib (Kawartha Cardiology Clinical Trials), Sam Henein (SKDS Research Inc.), David Kendler (Prohealth Clinical Research Centre), Hasnain Khandwala (LMC Clinical Research Inc. (Etobicoke)), Pierre Lachance (Clinique Medicale St-Louis (Recherche) inc d/b/a/ Centre de Recherche Saint-Louis), Jean-Pierre Lavoie (Centre de Dépistage et Recherche Cardiovasculaire Rive-Sud), Gilles Ouellet (Recherches Cliniques Theradev), Dennis Rupka (Fraser Clinical Trials Inc.), David Twum-Barima (LMC Clinical Research Inc. (Oakville)), Saul Vizel (Dr. Saul Vizel Cardiac Research Office), **China**, Shiping Cao (NanFang Hospital), Yingru Chai (Second Hospital of Shanxi Medical University), Buxing Chen (Beijing Tiantan Hospital), De Chen (Yangpu Hospital, Tongji University), Hong Chen (Peking University Peoples Hospital), Jiyan Chen (The People's Hospital of Guangxi Zhuang Autonomous Region), Yuanlu Chen (TEDA International Cardiovascular Hospital), Lu Fu (The First Affiliated Hospital of Harbin Medical University), Xueya Guo (Beijing Anzhen Hospital), Yong He (West China Hospital, Sichuan University), Jing Huang (The Second Affiliated Hospital of Chongqing Medical University), Lun Huang (Jilin Central General Hospital), Shian Huang (Affiliated Hospital of Guangdong Medical University), Shaobin Jia (General Hospital of Ningxia Medical University), Weihong Jiang (The Third Xiangya Hospital of Central South University), Tianfa Li (The First Hospital of Jilin University), Xiang Li (Yanbian University Hospital), Yanbing Li (The First Affiliated Hospital, Sun Yat-sen University), Yingzhong Lin (The People's Hospital of Guangxi Zhuang Autonomous Region), Feng Liu (Suzhou Kowloon Hospital Shanghai Jiaotong University Medical School), Ming Liu (General Hospital of Tianjin), Zongjun Liu (Shanghai Putuo District Central Hospital), Mingzhi Long (Nanjing Medical University Affiliated 2nd Hospital), Ming Luo (Tongji Hospital of Tongji University), Huyati Mu (The First Affiliated Hospital of Xinjiang Medical University), Wenyue Pang (Shengjing Hospital of China Medical University), Daoquan Peng (The 2nd Xiangya Hospital of Central South University), Yuemin Sun (Tianjin Medical University General Hospital), Xiaoyue Wang (Yueyang First People's Hospital), Zhirong Wang (The Affiliated Hospital of Xuzhou Medical College), Yanqing Wu (The Second Affiliated Hospital of Nanchang University), Jinchuan Yan (Affiliated Hospital of Jiangsu University), Ping Yang (China-Japan Union Hospital of Jilin University), Zuyi Yuan (The First Affiliated Hospital of Xi'an Jiaotong University), Aidong Zhang (The first affiliated hospital of Jinan University), Keqin Zhang (Shanghai Tongji Hospital), Xuelian Zhang (Jilin Province People's Hospital), Yuan Zhang (Inner Mongolia People's Hospital), Qiang Zhao (Ruijin Hospital, Shanghai Jiaotong Uni. School of Med.), Xingshan Zhao (Beijing Jishuitan Hospital), **Czech Republic**, Lubomir Ballek (Kardiologie JH s.r.o.), Petr Barton (Poliklinika Chocen a.s.), Jana Cepova (Fakultni nemocnice v Motole), Zdenek Coufal (Krajska nemocnice T. Bati a.s.), Richard Ferkl (Kardiologicka ambulance MUDr. Ferkl s.r.o.), Jan Hubac (MUDr. Jan Hubac s.r.o.), Vera Klokocnikova (CLINTRIAL s.r.o.), Ondrej Ludka (MUDr. Alexandra Ludkova), Emilia Malicherova (ResTrial s.r.o.), Dagmar Malotova (CTCenter MaVe s.r.o.), Jiri Matuska (MATMED s.r.o.), Martin Peterka (Nemocnice Slany), Jana Pisova

(Kardio-Pisova s.r.o.), Lea Raclavska (Medicentrum Beroun spol. s.r.o.), Ivan Rihacek (Fakultni nemocnice u sv. Anny v Brne), Jiri Skopek (Thomayerova nemocnice), Michal Smid (MUDr. Michal Smid kardiologicka ambulance), Miroslav Solar (Fakultni nemocnice Hradec Kralove), Rene Turcinek (DIAINT spol. s r.o.), Jan Vaclavik (Kardio Vaclavik s.r.o.), Petr Vodnansky (PV - kardiologie s.r.o.), Eva Zidkova (Corintez s.r.o.), **Denmark**, Lia Bang (Rigshospitalet), Kenneth Egstrup (OUH), Gunnar Gislason (Gentofte Hospital), Ib Klausen (Regionshospitalet Viborg), Børge Nordestgaard (Herlev Hospital), Erik Schmidt (Aalborg University Hospital), Henrik Wiggers (Skejby Sygehus - Aarhus University Hospital), **Estonia**, Ülle Jakovlev (East Tallinn Central Hospital), Jüri Kaik (Fertilitas AS), Rein Kolk (Tartu University Hospital), Riin Lanno (Merelahe Family Doctors Centre), Arvo Rosenthal (Dr. Arvo Rosenthal LLC), Liina Viitas (Liina Viitas OÜ), Mihhail Zemtsovski (West Tallinn Central Hospital), **Hungary**, Timea Balo (Simmelweis Egyetem), Tivadar Banyai (Synexus Magyarország Egészségügyi Szolgáltató Kft.- Gyula DRS), Tamas Barany (Clinexpert Kft.), Katalin Bezzegh (DRC Gyogyszervizsgalo Kozpont Kft.), Timea Csaszar (Mazso-Pharma Kutatas-fejlesztési Kft.), Beata Csepregi (Nyiro Gyula Orszagos Pszichiatriai es Addiktologiai Intezet), Istvan Edes (Edes Szivunk Egészségközpont Kft.), Zsuzsanna Feher (Synexus Magyarország Kft.), Tibor Fulop (Debreceni Egyetem), Eleonora Harcsa (Markhot Ferenc Oktatókórház es Rendelőintezet), Richard Horthy (Dr. Kenessey Albert Kórház-Rendelőintezet), Krisztian Kiss (Meditoll Kft.), Robert Gabor Kiss (Magyar Honvédség Egészségügyi Központ), Laszlo Konyves (Lausmed Kft.), Imre Kovacs (Soproni Erzsébet Oktató Kórház es Rehabilitációs Intezet), Ferenc Lakatos (Belgyógyászati es Kardiologiai Magánrendelő), Botond Literati-Nagy (DRC Balatonyorok), Andras Matoltsy (Kanizsai Dorottya Kórház), Bela Merkely (Simmelweis Egyetem), Margit Mileder (Csolnoky Ferenc Kórház), Janos Mucsi (Erzsébet Gondozóház Kft.), Laszlo Nagy (Csongrad Megyei Dr. Bugyi Istvan Kórház), Lajos Ocsko (Mohácsi Kórház), Tamas Oroszlan (Zala Megyei Szent Rafael Kórház), Gyorgy Paragh (Debreceni Egyetem), Istvan Reiber (Fejér Megyei Szent György Egyetemi Oktató Kórház), Csaba Salamon (Clinfan Szolgáltató Kft.), Judit Simon (CSALADGYOGYASZ Kft.), Imre Szakal (Selye Janos Kórház), Szabolcs Szepesvari (Kiskunhalasi Semmelweis Kórház), Imre Ungi (Szegedi Tudományegyetem Szent-Györgyi Albert Klinikai Központ), Sandor Vangel (Belinus Bt.), Zsuzsanna Varga (BKS Research Kft.), Szilard Vasas (BORBANYA PRAXIS Kft.), Karoly Wittmann (Synexus Magyarország Egészségügyi Szolgáltató Kft.- Zalaegerszeg AS), Zsolt Zilahi (Medifarma-98 Kft.), Szilard Zolyomi (Kalocsai Szent Kereszt Kórház), Marianna Zsom (Principal SMO Kft.), **Italy**, Elena Alberghini (Ospedale Bassini), Emilio Assanelli (Centro Cardiologico Monzino-IRCCS), Riccardo Bonadonna (Azienda Ospedaliera Universitaria di Parma), Claudio Borghi (Azienda Ospedaliera Universitaria Policlinico Sant'Orsola Malpighi), Maria D'Avino (Azienda Ospedaliera di Rilievo Nazionale A. Cardarelli), Salvatore De Cosmo (IRCCS Ospedale Casa Sollievo della Sofferenza), Giuseppe Derosa (Fondazione IRCCS Policlinico San Matteo), Giovanni Esposito (Azienda Ospedaliera Universitaria "Federico II"), Claudio Ferri (ASL 1 Avezzano L'Aquila Sulmona- Ospedale Regionale San Salvatore), Davide Lauro (Azienda Ospedaliera Universitaria Policlinico Tor Vergata), Carmine Mazzone (Azienda Servizi Sanitari 1 Triestina), Giuliana Mombelli (Azienda Socio Sanitaria Territoriale Niguarda (Grande Ospedale Metropolitano Niguarda)), Savina Nodari (Azienda Socio Sanitaria Territoriale degli Spedali Civili di Brescia (Presidio Spedali Civili)), Angelina Passaro (Azienda Ospedaliera Universitaria Arcispedale Sant'Anna), Piermarco Piatti (Ospedale San Raffaele), Michele Senni (Azienda Socio

Sanitaria Territoriale Papa Giovanni XXIII), **Japan**, Kenji Ando (Kokura Memorial Hospital), Tetsuo Betsuyaku (Tokyo Tenshi Hospital), Hiroshi Domae (Tokushukai Tokyo-Nishi Tokushukai Hospital), Kenshi Fujii (Watanabeigakukai Sakurabashi Watanabe Hospital), Shigeru Fujii (Chiyukai Fukuoka Shinmizumaki Hospital), Yasushi Fukushima (Fukuwa Clinic), Yoshiki Hata (Kenshinkai Minamino Cardiovascular Hospital), Nobuyoshi Higa (Okinawa Tokushukai Chubu Tokushukai Hospital), Shinichi Higashiue (Tokushukai Kishiwada Tokushukai Hospital), Mitsugu Hirokami (Teine Keijinkai Clinic), Munehiro Honda (KKR Mishuku Hospital), Tomoaki Ishigami (Yokohama City University Hospital), Hiroshige Itakura (IHL Shinagawa East One Medical Clinic), Toshiaki Kadokami (Fukuokaken Saiseikai Futsukaichi Hospital), Takashi Kageyama (Tokai Memorial Hospital), Tsunekazu Kakuta (Tsuchiura Kyodo General Hospital), Mitsuaki Katsuta (Kyojinkai Gosyono Hikari Clinic), Kazuya Kawai (Chikamorikai Chikamori Hospital), Hideo Kawakami (Ehime Prefectural Imabari Hospital), Arihiro Kiyosue (Tokyo-Eki Center-Building Clinic), Takehiko Kuramochi (Okinawa Tokushukai Chibanishi General Hospital), Kazuyuki Masamoto (Keiaikai Saga Memorial Hospital), Katsuhiko Matsuda (MATSUDA Cardiovascular Clinic), Otoyama Miho (Yuhokai Miho Clinic), Naomasa Miyamoto (Sanyukai Saino Clinic), Makoto Murata (Gunma Prefectural Cardiovascular Center), Takeo Naito (Keiseikai Goshi Hospital), Masahiko Nakamura (Matsumoto City Hospital), Yuichiro Nakamura (Nakamura Cardiovascular Clinic), Hiroyuki Oda (Public Central Hospital of Matto Ishikawa), Takafumi Oga (Shinjuku Research Park Clinic), Munenori Okubo (Gifu Heart-center), Hisakuni Sekino (Sekino Hospital), Shu Suzuki (Tohoku Kosai Hospital), Natsuki Takahashi (Matsuyama Shimin Hospital), Shinichi Takase (Seneikai Takase Clinic), Michinao Tan (Tokeidai Memorial Clinic), Ikuta Tanaka (Takamatsu Municipal Hospital), Imun Tei (Eiyukai Ayase Heart Clinic), Muneatsu Toshima (Kenshinkai Niitsu Medical Center Hospital), Mitsuru Tsujimoto (Shinshinkai The Veritas Hospital), Kengo Tsukahara (Fujisawa City Hospital), Takashi Tsutsui (Gokeikai Osaka Kaisei Hospital), Yota Urakabe (Keiwakai Oita Oka Hospital), Yasushi Wakida (Daishinkai Ookuma Hospital), Takayuki Watanabe (Yokohama City Minato Red Cross Hospital), Manabu Yamamoto (Adachi Kyosai Hospital), Hidekatsu Yanai (Kohndai Hp., National Center for Global Health and Medicine), Hirokazu Yokoi (Rakuwakai Otowa Hospital), **Lithuania**, Jurate Anusauskiene (Klaipeda Republican Hospital, Public Institution), Jolita Badariene (Vilnius University Hospital Santariskiu Clinic, Public Institution), Leone Cepinskiene (Kaunas Clinical Hospital, Public Institution), Valdas Dobilas (Klinikiniai sprendimai, JSC), Roma Kavaliauskiene (Cardiology and Rehabilitation Clinic, JSC), Jurgita Plisiene (Siauliai Republican Hospital, Public Institution), Rimvydas Slapikas (Hospital of Lithuanian University of Health Sciences Kaunas Clinics), Danute Strazdiene (Klinikiniai sprendimai, JSC), Egle Urbanaviciene (Kaunas Silainiu Outpatient Clinic, Public Institution), Audrone Urboniene (Saules Seimos Medicinos Centras, JSC), Lina Venceviciene (Vilnius University Hospital Santaros Klinikos, Public Institution), **Mexico**, Cesar Gonzalo Calvo Vargas (Diseño y Planeacion en Investigacion Medica S.C.), Manuel Odin de los Rios Ibarra (Centro para el Desarrollo de la Medicina y de Asistencia Medica Especializada S.C.), Luis Fernando Flota Cervera (Sociedad de Cirugia Vascular Plastica Reconstructiva de Angiologia y Cardiologia SCP), Carlos Alberto Guizar Sanchez (Clistile, S.A. de C.V.), Jesus Jaime Illescas Diaz (Unidad de Investigacion Clinica Cardiometabolica de Occidente S.C.), Oscar Martin Lopez Ruiz (Phylaxis Clinicas Research S. de R.L. de C.V.), Luis Alejandro Nevarez Ruiz (INVESTIGACION EN SALUD Y METABOLISMO S.C.), Francisco Gerardo Padilla Padilla (Cardiologia Clinica e

Intervencionista), Hector Tamez Perez (Centro Medico San Francisco), Raul Gerardo Velasco Sanchez (Hospital Dr. Angel Leño), **Netherlands**, Mazin AlHakim (EB Medical Research), Mazin AlHakim (EB Utrecht), Harry Crijns (Maastricht University Medical Center), Edwin de Melker (Onze Lieve Vrouwe Gasthuis, Locatie West), Frank den Hartog (Gelderse Vallei Ziekenhuis, Ede), Bjorn Groenemeijer (Gelre Ziekenhuizen, Apeldoorn), Simone Hartong (Albert Schweitzer Ziekenhuis, Dordwijk), Walter Hermans (ETZ Elisabeth), Bastiaan Kietselaer (Zuyderland Medisch Centrum - Heerlen), Adrianus Kuijper (Spaarne Gasthuis, Hoofddorp), Gerardus Linssen (Ziekenhuisgroep Twente, Almelo), Houshang Monajemi (Rijnstate), Pieter Nierop (Franciscus Gasthuis), Anthonius Oude Ophuis (Canisius - Wilhelmina Ziekenhuis), Jacobus Plomp (Tergooiziekenhuizen, Hilversum), Johannes Post (Catharina Ziekenhuis Eindhoven), Gloria Rojas Lingan (Andromed Eindhoven), Eelko Ronner (Reinier de Graaf Gasthuis), Erik Stroes (Amsterdam UMC, Locatie AMC), Hendrik Swart (D & A Research), Roland Troquay (VieCuri Medisch Centrum), Eugene van Beek (Ziekenhuis St. Jansdal), Paul van Bergen (Vasculair Onderzoek Centrum), Vivienne van de Walle (PreCare Trial & Recruitment), Robert Van der Heijden (Franciscus Vlietland), Willem Van Kempen (Andromed Rotterdam), Rudolf van Leendert (Albert Schweitzer Ziekenhuis, Zwijndrecht), Frank Visseren (UMC Utrecht), **New Zealand**, Jocelyne Benatar (Auckland City Hospital), Simon Carson (Southern Clinical Trials Beckenham, Christchurch), Renate Koops (Middlemore Hospital), Jeremy Krebs (Wellington Hospital), John Richmond (Southern Clinical Trials, Waitemata), Nine Smuts (P3 Research Limited (Hawkes Bay)), Richard Troughton (Christchurch Hospital NZ), Michael Williams (Lakeland Clinical Trials), **Poland**, Karolina Antkowiak-Piatyszek (Synexus Polska sp. z o.o. Oddzial w Poznaniu), Krzysztof Cymerman (Indywidualna Specjalistyczna Praktyka Lekarska w Dziedzinie Kardiologii lek. med. Krzysztof Cymerman), Ewa Czernecka (Synexus Polska Sp. z o.o. Oddział w Warszawie), Ewa Domanska (Centrum Medyczne CDS), Marek Dwojak (Synexus Polska Sp. z o.o. Oddział we Wrocławiu), Marcin Fijalkowski (Uniwersyteckie Centrum Kliniczne), Bohdan Firek (NZOZ HEUREKA), Jaroslaw Jurowiecki (Poradnia Kardiologiczna Jarosław Jurowiecki), Barbara Kaczmarek (POLIMEDICA Centrum Badań Profilaktyki i Leczenia), Piotr Karas (KO-MED Centra Kliniczne Lublin II), Marek Konieczny (KO-MED), Maciej Kosmider (Prywatny Gabinet Kardiologiczny Dr n.med.Maciej Kosmider), Maciej Kozina (NZOZ Lecznico-Rehabilitacyjny Ośrodek Medycyny Rodzinnej), Elzbieta Kramarczuk (KO-MED Centra Kliniczne Zamosc), Jolanta Krzykowska (Synexus Polska Sp. z o.o. Oddzial w Gdyni), Ewa Krzyzagorska (Praktyka Lekarska Ewa Krzyzagorska), Monika Kuligowska-Jakubowska (Synexus Polska SCM Sp. z o.o. Gdansk), Wlodzimierz Kus (Indywidualna Specjalistyczna Praktyka Lekarska), Lech Lazuka (Prywatny Gabinet Lekarski Lech Lazuka), Stanislaw Mazur (Centrum Medyczne Medyk), Pawel Miekus (NZOZ Pro-Cordis Sopockie Centrum Bad. Kardiolog.), Nonna Anna Nowak (ClinicMed Daniluk, Nowak Spółka Jawna), Marcin Ogorek (NZOZ ALL-MED Centrum Medyczne Specjalistyczne Gabinety Lekarskie), Jakub Ostrowski (KARDIOMED Janczka Kociwska Ostki PodckaRekrzSp), Grazyna Popena (B_SERWIS POPENDA SP.JAWNA), Piotr Rozpondek (Krakowskie Centrum Medyczne Sp. z o.o.), Janusz Spyra (NZOZ Przychodnia Specjalistyczna H. Rudzki, A. Wittek), Jaroslaw Trebacz (Centrum Medyczne Zdrowa J. Trębacz W. Zajdel s.j.), Renata Wnetrzak-Michalska (Synexus Polska Sp. z o.o. Oddzial w Katowicach), Katarzyna Zelazowska (KO-MED Centra Kliniczne Staszow), Witold Zmuda (Medicome Sp. z o.o.), **Russia**, Natalia Afanasieva (Nebbiolo LLC), Evgeniya Akatova (SBEI HPE "Moscow State Medical and Dentistry University

n.a. A. I. Evdokimov" of the MoH of the RF), Olga Barbarash (FSBI "Scientific-research Institute for Complex Problems of cardiovascular disease"), Dmitry Belenky (SBIH of Novosibirsk Region "Clinical Emergency Hospital #2"), Galina Chumakova (TSHI "Altay Territorial Cardiological dispensary"), Dmitry Dronov (BIH of Omsk region "Clinical Medico-Sanitary Unit # 9), Olga Ershova (SAIH of Yaroslavl region "Clinical Hospital of Emergency Medical Care n.a. N. V. Solovyev"), Larisa Khaisheva (City Emergency Hospital #2), Vladimir Khirmanov (FFSBI "The Nikiforov Russian Center of Emergency and Radiation Medicine"), Natalya Koziolova (SHI "Perm Regional Hospital of War Veterans"), Liudmila Kvitkova (SAIH "Kemerovo Regional Clinical Hospital"), Roman Libis (FSBEI HE Orenburg State Medical University of the MoH of the RF), Konstantin Likhomanov (FSBI "Research Institute for Cardiology" of Siberian Branch RAMS), Maria Mozheiko (Yaroslavl Regional Clinical Hospital of War Veterans), Konstantin Nikolaev (MIH City clinical Hospital #34), Andrey Obrezan (LLC "International Medical Center "SOGAZ"), Aleksey Panov (FSBI North-West Federal Medical Research Center n.a. V.A. Almazov of MoH RF), Zhanna Sizova (FSAEI HE " First Moscow State Medical University n.a. I.M. Sechenov" of the MoH of the RF), Raisa Stryuk (SBEI HPE "Moscow State Medical and Dentistry University n.a. A. I. Evdokimov" of the MoH of the RF), Igor Suchkov (SBEI HPE " Ryazan State Medical University n.a. Academician I.P. Pavlov" of the MoH of the RF), Andrey Susekov (FSBEI APE " Russian Medical Academy of Continuous Postgraduate Education" of the MoH of the RF), Nikolay Tarasov (FSHI "MSU of MoIA of RF of Kemerovo Region"), Soreya Urazgildeeva (FSBHI Clinical Hospital No. 122 named after L.G. Sokolov of the FMBA), Yuri Vasyuk (SBEI HPE "Moscow State Medical and Dentistry University n.a. A. I. Evdokimov" of the MoH of the RF), Arkady Vertkin (SBEI HPE "Moscow State Medical and Dentistry University n.a. A. I. Evdokimov" of the MoH of the RF), Alexander Vishnevsky (SPb SBIH "City Pokrovskaya Hospital"), Mikhail Voevoda (FSBSI "Scientific Research Institute of Therapy and Preventive Medicine"), Polina Yakhontova (SBIH of Novosibirsk region " Novosibirsk Regional Clinical Cardiological Dispensary"), **South Africa**, Luthando Adams (LCS Clinical Research Unit), Susan Arnold (Excellentis Clinical Trial Consultants), Qasim Bhorat (Soweto Clinical Trials Centre), Dirk Blom (Groote Schuur Hospital Lipid Laboratory), Johannes Breedts (Emmed Research), Kathleen Coetzee (Paarl Research Centre), Fared Dindar (Drs Dindar and Partners), Mahesh Duki (Dr M Duki Research and Trial Site), Johannes Engelbrecht (Dr JM Engelbrecht Practice), Nyda Fourie (Iatros International), Muhammed Fulat (Clinical Trial Systems), Vimladhevi Govender (Westcliff Research Centre), Uttam Govind (Randles Road Medical Centre), Gerbrand Haasbroek (Somerset West Clinical Trial Unit), Yasser Jooma (Mzansi Ethical Research Centre), Jaco Jurgens (DJW Research), Ynez Kelfkens (Kelfkens, Y), Hester Kotze (Medipark Centre for Clinical Research), Johannes Lombaard (Josha Research), Landman Lombard (Cape Town Medical Research Centre), Akbar Mahomed (Dr AA Mahomed Medical Centre), Daniel Malan (PHOENIX Pharma (Pty) Ltd), Mokgadi Mogashoa (Botho ke Bontle Health Services), Sehulong Moraba (Synexus SA - Stanza Clinical Research Centre), Leya Motala (MERC - Cape Town), Helena Oosthuizen (Oosthuizen, Helena), Wessels Oosthuysen (Limaro Research), Kirsten Peacey (Synexus Helderberg Clinical Research Centre), Perumal Pillai (Pillai, P), Gracjan Podgorski (Podgorski, GP), Elsje Potgieter (Synexus SA Watermeyer Clinical Research Centre), Hans Prozesky (Tread Research), Jeevren Reddy (Reddy, J), Mary Seeber (Seeber, M), Eugene van der Walt (Medicross Roodepoort Clinical Research), Louis van Zyl (Clinical Projects Research SA (PTY) LTD), Norbert Welkovic (Johese Clinical Research:

Midstream), **South Korea**, Hyun-Jai Cho (Seoul National University Hospital), Wook Sung Chung (The Catholic University of Korea, Seoul St. Mary's Hospital), Seung Hwan Han (Gachon University Gil Medical Center), Myung Ho Jeong (Chonnam National University Hospital), Chong-Jin Kim (Kyung Hee University Hospital at Gangdong), Dong Bin Kim (The Catholic University of Korea, St. Paul's Hospital), Dong-Soo Kim (Inje University Busan Paik Hospital), Moo Hyun Kim (Dong-A University Hospital), Sang Hyun Kim (Seoul Metropolitan Government Seoul National University Boramae Medical Center), Young-Hak Kim (Asan Medical Center), Sang Kon Lee (Ulsan University Hospital), Sang-Hak Lee (SEVERANCE HOSPITAL, YONSEI UNIVERSITY), Soo Lim (Seoul National University Bundang Hospital), **Taiwan**, Chern-En Chiang (Taipei Veterans General Hospital), Chi-Hung Huang (Cathay General Hospital), Wen-Ter Lai (Kaohsiung Medical University Chung-Ho Memorial Hospital), Thung-Lip Lee (E-DA Hospital), Kou-Gi Shyu (Shin Kong Wu Ho-Su Memorial Hospital), Chih-Yuan Wang (National Taiwan University Hospital), **Ukraine**, Liudmila Alieksieieva (Kjiv City Oleksandrivska Clinical Hospital), Volodymyr Bezv (Medical Center of PE First Private Clinic), Ivan Chohey (CI UDH Dept of Ther SHEI Fac of PGE&Pre-Univ Training), Oleksandra Donets (Medical Center of LLC Medbud-Clinic), Ivan Fushtey (CNE CCH#10 Dept of Therapy SI ZMA of PGE MOH), Oleksandr Golovchenko (Medical Clinical Investigational Center Medical Center LLC Health Clinic), Olga Gyrina (LLC Treatment and Diagnostic Center Adonis Plus), Oleksandr Karpenko (Kyiv City Clinical Hospital #1), Mykola Kopytsya (State Institution LT Malaya Inst. of Ther. of AMS of Ukraine), Oleksii Korzh (MC Doctor Alex Dept of General Practice-Family Medicine Kharkiv MA of PGE), Volodymyr Koshlia (CI Zaporizhzhia City Multifield CH #9, Dept of Therapy, SI ZMA of PGE of MoHU), Valentyna Koval (Municipal the 8-th CCH), Oleksandr Kovalov (SI National Scientific Centre of Radiation Medicine of NAMSU), Igor Kraiz (Railway Transport Kharkiv CH #1 of Healthcare Center Branch of PJSC Ukr Railway), Anna Kulyk (CI Cherkasy RH of Cherkasy Regional Council), Iryna Kupnovytska (CI Ivano-Frankivsk Reg CI Card Center Dept of Arterial Hypertension SHEI Ivano-Frankivsk NMU), Mykola Kushnir (Zhytomyr regional clinical hospital n.a. O.F. Gerbachevskyy), Yurii Lymar (CNI Consultative and Diagnostic Center of Desnianskyi District of Kyiv), Viktor Lyzogub (Kyiv CCH #12 Dept of Therapy O.O.Bogomolets NMU), Valeriy Molodtsov (City Hospital #1), Halyna Myshanych (Kyiv CH on Railway Transport #2 of Branch Center of Healthcare Public Company Ukr Railway), Oleksandr Parkhomenko (SI NSC M.D. Strazhesko Institute of Cardiology of NAMSU), Leonid Rudenko (Kyiv City Clinical Hospital of Emergency Medical Care), Iurii Rudyk (GI L.T.Malaya Therapy National Institute of the NAMS of Ukraine), Sergii Serik (GI L.T.Malaya Therapy National Institute of the NAMS of Ukraine), Sergii Shevchuk (SRI of Invalid Rehabilitation (EST Complex) of Vinnytsia M.I.Pyrogov NMU MOHU), Inna Sorokina (MC of PHEI Institute of General Practice - Family Medicine), Mykola Stanislavchuk (Vinnytsia M.I.Pyrogov RCH Dept of cardiology Vinnytsia M.I.Pyrogov NMU), Yevgeniya Svyshchenko (SI NSC M.D. Strazhesko Institute of Cardiology of NAMSU), Oleg Sychov (M.D. Strazhesko Institute of Cardiology of AMS of Ukraine), Nadiya Tryshchuk (Educative -Sc Med Complex University Clin of Kharkiv NMU, Dept of Therapy, Nat Pharmaceutical University), Vira Tseluyko (CNE City Clin Hosp #8 of KCC Dept of Cardiology for Patients with MI #2 Kharkiv MA of PGE of MOHU), Myroslava Vayda (Transcarpathian Regional Clinical Cardiology Dispansery), Valeriy Vdovychenko (Communal City Clinical Hospital of Ambulance, Dept of Therapy #1 D.Halytskyi Lviv NMU), Andriy Yagensky (CI Lutsk City Clinical Hospital Volyn Regional Center

of Cardiovascular Pathology & Thrombolysis), Larysa Yena (SI D.F.Chebortariov Institute of Gerontology of NAMSU), Vyacheslav Zhdan (M.V. Sklifosovskyi Poltava RCH Dept of Rheumatology HSEIU UMSA), Svitlana Zhurba (Cherkasy Regional Cardiological Center), **United Kingdom**, Gerald Clesham (Broomfield Hospital), Susannah Eyre (Synexus Merseyside Clinical Research Centre), Michael Fisher (Royal Liverpool University Hospital), Shalini Iyengar (Synexus Hexham General Hospital), Arham Jamal (Synexus Thames), Honer Kadr (Queen's Hospital), Philip Keeling (Torbay Hospital), Christina Kyriakidou (Synexus Birmingham Clinical Research Centre), Terry Levy (Royal Bournemouth General Hospital), Imrozia Munsoor (Synexus Scotland Clinical Research Centre), David Newby (Royal Infirmary of Edinburgh), Alastair Pell (Monklands Hospital), Mahadev Ramjee (Synexus Lancashire Clinical Research Centre), Adrian Renouf (Royal Devon and Exeter Hospital (Wonford)), Manish Saxena (Barts Hospital), David Smith (Morrison Hospital), Hawys Thomas (Synexus Wales Clinical Research Centre), Madhu Venkate Gowda (Synexus Manchester Clinical Research Centre), Adam Viljoen (Lister Hospital), Robin Weir (Hairmyres Hospital), **United States**, Michael Adams (Synexus Clinical Research US, Inc.), Amer Al-Karadsheh (The Endocrine Center, Ltd, LLP), Mohammed Allaw (Synexus Clinical Research US, Inc.), Dario Altamirano (AGA Clinical Trials), James Andersen (Meridien Research), Nabil Andrawis (Manassas Clinical Research Center), Mehrdad Ariani (Valley Clinical Trials, Inc.), Brian Asbill (Asheville Cardiology Associates, PA), Michael Azorr (Columbia Research Group), Chris Bajaj (Diabetes and Thyroid Center of Fort Worth), Claire Baker (Diabetes and Endocrine Associates, P.C.), Pelbreton Balfour (Cardiology Consultants), Kim Barbel-Johnson (Care Partners Clinical Research, LLC), Cathy Barnes (Suncoast Clinical Research Inc.), Linda Bassett Shaftoe (PMG Research of Rocky Mount, LLC), Michael Bauer (Northwest Heart Specialists), Seth Baum (Integrated Heart Care), Harold Bays (L-MARC Research Center), David Becker (Chestnut Hill Cardiology, Ltd.), Kevin Bender (DBC Research, Corp), Robert Benton (Capital Cardiology Associates), Ramon Berenguer (Florida Medical Center & Research Inc), Barry Bertolet (Cardiology Associates of North Mississippi), C David Bird (Synexus Clinical Research US, Inc.), Kenneth Blaze (South Broward Research, LLC), Fernando Bocalandro (Permian Research Foundation), Donald Brandon (California Research Foundation), Ronald Brenner (Neurobehavioral Research, Inc.), Robert Broker (Hillcrest Clinical Research, LLC), Alan Brown (Advocate Health and Hospitals Corporation), Alan Brown (Advocate-Naperville), Todd Brown (University of Alabama), Tami Bruce (Synexus Clinical Research US, Inc.), Robert Busch (Albany Medical College), Michael Butcher (Sterling Research), Robert Buynak (Buynak Clinical Research), Kevin Cannon (Wilmington Health), James Carswell (Clinical Research of Charleston), Deanna Cheung (Long Beach Center for Clinical Research), Keith Chu (Inova Schar Cancer Center), Robert Cohen (Cohen Medical Research Associates, LLC), William Collis (Parkview Research Center), Jonathan Condit (American Health Network of Indiana, LLC), Terence Connelly (Charlotte Heart & Vascular Institute, PA), Erin Cooksey (Synexus Clinical Research US, Inc.), George Cornett (American Health Network of Indiana, LLC), Brian Curtis (Corvallis Clinic PC), Nizar Daboul (Advanced Medical Research), Georges Dagher (Heart & Vascular Institute FL), David Davidson (NorthShore University HealthSystem), Cedrice Davis (Urban Family Practice Associates, PC), Michael Denenberg (Clinical Research of Rock Hill), Donna DeSantis (Synexus Clinical Research US, Inc.), Michael Deucher (Southwest General Health Center), James Diener (Cadillac Clinical Research, LLC), Tyler Dixon (Ericksen Research & Development, LLC), Sean Donahoe (Northwell Health

Physician Partners Cardiology), Daniel Duprez (Regents of the University of Minnesota), Samuel Durr (Black Hills Cardiovascular Research), Samuel Durr (Regional Health Research), John Earl (PMG Research of Hickory, LLC), Frank Eder (Regional Clinical Research / United Medical Associates), Gary Elkin (IACT Health), William Ellison (Synexus Clinical Research US, Inc.), Brian Everhart (Heritage Valley Medical Group Inc.), Cecil Farrington (PMG Research of Salisbury, LLC), Lawrence Feld (Horizon Clinical Research Associates, PLLC), Michael Feldman (Homestead Medical Research), Jonathan Fialkow (Cardiovascular Research Center of South Florida), Thomas Fiel (Fiel Family and Sports Medicine, PC), Gregory Flippo (Alabama Clinical Therapeutics, LLC), Malcolm Foster (Metro Knoxville HMA, LLC), Miguel Franco (MCA Research), Brad Frandsen (Sound Medical Research), Nashwa Gabra (Burke Internal Medicine & Research), Bernard Garcia (InvesClinic), Bernard Garcia (Hallandale Medical Center), Linda Gaudiani (Marin Endocrine Care and Research, Inc), Mark Gelernt (Cardiovascular Associates of the Delaware Valley), Steven Geller (Centennial Medical Group, PC), Chandra Ghosh (Laureate Medical Group at Northside, LLC), Son Giep (Plano Internal Medicine Associates), Jason Go (Altru Clinic Main), David Godwin (VitaLink Research-Greenville), Gary Goldstein (Suncoast Clinical Research Inc.), Glenn Gould (Burke Primary Care), Gerald Greer (Arkansas Cardiology Clinic, PA), Carl Griffin (Lynn Health Science Institute), Vishal Gupta (Western Michigan University Homer Stryker M.D. School of Medicine Center for Clinical Res), Stephen Halpern (Synexus Clinical Research US, Inc.), Ihab Hamzeh (Ben Taub General Hospital), Michael Han (Southview Medical Group), Yehuda Handelsman (Metabolic Institute of America), Terence Hart (Terence T. Hart, MD), Walter Herbert Haught (Heart Center Research, LLC), William Haynos (Geisinger Clinic), David Headley (Planter's Clinic), David Herrington (Wake Forest University Baptist Medical Center), Maynard Holgado (Maynard Holgado, LLC), Timothy Howard (Medical Affiliated Research Center, Inc.), Carlos Hubbard (Cleveland Cardiovascular Research Foundation), Carlos Hubbard (Cleveland Clinic-Beachwood), John Hunter (Santa Rosa Cardiology Medical Group, Inc.), Donald Hurley (Medical Research South), Carlos Ince (Maryland Cardiovascular Specialists), Anthony Inzerello (Synexus Clinical Research US, Inc.), Bruce Iteld (Louisiana Heart Center), Bruce Iteld (Louisiana Heart Center), Ravi Iyer (Nova Health Management & Research Group, PC), Ashit Jain (California Cardiovascular Cnslt), Michael Jardula (Desert Oasis Healthcare), Preetham Jetty (Community Hospital of Anderson and Madison County, Inc.), Staci Jordan (Overland Park Surgical Specialties, LLC d/b/a College Park Family Care Center Physicians Group), Parag Joshi (University of Texas Southwestern Medical Center), Mario Juarez (Panacea Clinical Research, LLC), Mayar Jundi (Covenant Medical Center, Inc.), Scott Kaiser (Synexus Clinical Research US, Inc.), David Kandath (Saratoga Springs Assoc., PC), Richard Kastelic (Richard M Kastelic, MD and Associates / Berkley Hills Clinicals), Jennifer Kay (INACTIVE- Synexus Clinical Research US, Inc.), Ajit Khaira (B & K Medical Research Center), Vipin Khetarpal (Michigan Cardiovascular Institute), William Kirby (Synexus Clinical Research US, Inc.), Geoffrey Kline (University of North Texas Health Science Center), Sarah Kohnstamm (VA Medical Center - Philadelphia), James Kopp (Synexus Clinical Research US, Inc.), Gary Korff (Synexus Clinical Research US, Inc.), Larry Kotek (Synexus Clinical Research US, Inc.), Victoria Kuohung (Beacon Clinical Research, LLC), German Larrain (Aspirus Research Institute), John Larry (Ohio State University), Samuel Lederman (Altus Research, Inc.), Gilbert Ledesma (Arlington Family Research Center), Daniel Lee (Bay Regional Medical Center), Peter Lee (Dean and St. Mary's Outpatient Center), Richard Leggett (Crossroads Clinical Research, LLC), Robert Lending

(Synexus Clinical Research US, Inc.), Thomas Lenzmeier (Synexus Clinical Research US, Inc.), Michael Lesko (Geisinger Gray's Woods Clinic), Lawrence Levinson (Tipton Medical & Diagnostic Center), Matthew Lewis (Synexus Clinical Research US, Inc.), Ronald Littlefield (Palmetto Research Center, LLC), Leif Lohrbauer (St. Luke's Cardiology), John Lowe (Advanced Research Institute), Sharan Mahal (Advanced Heart Care, LLC), Padma Mangu (Sterling Research), Vernon Mascarenhas (Geisinger Wyoming Valley Medical Center), Charles Mathis (Midwest Cardiovascular Research and Education Foundation), Ronald Mayfield (Mountain View Clinical Research, Inc.), Maureen Mays (Portland Preventive Cardiology), Tegan McCormick (Christie Clinic, LLC), John McGettigan (Quality of Life Medical & Research Center, LLC), Mark McKenzie (WR-ClinSearch, LLC), Mary Ann McLaughlin (Mount Sinai - PRIME), Thomas Meyer (Strootbants Cardiovascular Center), Gary Miller (Cardiology Consultants of Danville, Inc.), Anthony Mills (Anthony Mills, MD, Inc.), Lubna Mirza (Lynn Institute of Norman), Umesh Mishra (WellSpan Cardiology), Paul Moore (Research Management, Inc.), Nabil Morcos (Apex Research Institute), David Morin (Holston Medical Group, P.C.), John Morytko (South Florida Research Group, LLC), Samuel Mujica Trenche (Alas Science Clinical Research), Linda Murray (Synexus Clinical Research US, Inc.), Derek Muse (BBCR Holdings LLC dba JBR Clinical Research -- Midvale Campus), Venkatesh Nadar (Capital Area Research, LLC), Joseph Newberg (Synexus Clinical Research US, Inc.), Paul Norwood (Valley Research), Thomas O'Connor (American Health Network of Indiana, LLC), Larry Odekirk (Lynn Institute of Denver), Shelby Olds (PMG Research of Bristol, LLC), John Pasquini (Presbyterian Novant Heart and Wellness Charlotte), Andres Patron (Andres Patron, D.O., P.A), Jonathan Paul (University of Chicago Medical Center), Walter Pharr (Medication Management, LLC), Kevin Pounds (Synexus Clinical Research US, Inc.), Richard Powell (Meridien Research), James Pritchard (Sentral Clinical Research Services, LLC), Ofsman Quintana (Valley Central Research, Inc.), George Raad (PMG Research of Charlotte, LLC), Michael Radin (Radin Cardiovascular Medical Group), Bhola Rama (Rama Research LLC), Steven Ramos (Health Texas Research Institute), Michael Rausch (Heartland Research Associates, LLC), Naveed Razzaque (Synexus Clinical Research US, Inc.), Larry Reed (HealthCare Research Network), Michael Renzi (Advocare Heights Primary Care), Margaret Rhee (Synexus Clinical Research US, Inc.), James Rider (Cardiology Associates of Bellin Health), James Ritzenthaler (Saint Charles Health System), Orlando Rivero (Global Research Solutions Corp), Jennifer Robinson (Lipid Research Clinic - University of Iowa), Kathryn Rohr (Maine Research Associates), Jeffrey Rosen (Clinical Research of South Florida, an AMR company), Lars Runquist (PMG Research of Charleston, LLC), Lars Runquist (PMG of Charleston-Mt Pleasant), Renee Sangrigoli (Doylestown Health Physicians), David Scott (Scott Research Center), Bruce Seaton (Research Institute of the Carolinas, PLC), John Sensenbrenner (Sensenbrenner Primary Care), Parag Shah (Capital Cardiology Associates), Gerald Shockey (Synexus Clinical Research US, Inc.), Sylvia Shoffner (PMG Research of Cary, LLC), Harvey Snyder (Cardiovascular Associates of the Delaware Valley), Daniel Soffer (Pennsylvania Heart & Vascular), Stanislaw Sojka (Methodist Physicians Clinic Heart Consultants), Joseph Soufer (Chase Medical Research, LLC), Joseph Soufer (Chase Medical Research LLC), Venkatraman Srinivasan (Allegheny Valley Hospital), Daniel Storey (American Health Network of Indiana, LLC), Stephen Straubing (Southeast Clinical Research, LLC), Ronald Stumbris (Healthcare Research Network III, LLC), Andrew Sumner (Lehigh Valley Heart Specialists), Nirmal Sunkara (Kalo Clinical Research), Naeem Tahirkheli (South Oklahoma Heart

Research Group), Tahir Tak (Mayo Clinic Health System), Ben Thomas (WR-Mount Vernon Clinical Research, LLC), James Thomas (Medical University of South Carolina (MUSC)), Peter Toth (CGHMC Rockfalls Clinic), Miguel Trevino (Innovative Research of West Florida, Inc.), Traci Turner (Metabolic & Atherosclerosis Research Center), Damaris Vega (Juno Research, LLC), Dilip Viswanath (Cardiovascular Associates of the Delaware Valley), Jan Vlach (Medical Research Associates at The Walk-In Clinic), Paul Wakefield (PMG Research of Knoxville), Paul Wakefield (PMG Research of Knoxville), Brian Way (State of Franklin Healthcare Associates, PLLC), Aaron Weaver (Cambridge Medical Trials), Kenneth Williams (Seton Medical Group), Jonathan Wilson (PMG Research of Winston-Salem, LLC), Michael Winnie (3rd Coast Research Associates), Wilson Wong (Arkansas Heart Hospital), Richard Zelman (Cape Cod Research Institute), Wenwu Zhang (Clinical Trials of America, Inc.).

Endpoint Definitions

Members of the CEC will adjudicate each potential blinded event, based on pre-specified definitions, and render an assessment as to whether the case represents a confirmed event (meeting an event definition with all necessary documentation), a non-event (does not meet the event definition and likely represents an alternative or nonevent diagnosis), or lacks sufficient documentation for confirmation of an event. The potential events to be adjudicated are defined below.

Discussion on June 20th 2019 with AZ and IQVIA the date of the initial/index MI or Stroke will be added to the Cardiovascular Death adjudication forms for fatal MIs and Strokes. Cases previously adjudicated will be re-reviewed to ensure the date of the initial/index event is captured. For cases adjudicated after the implementation of this charter, CEC will adjudicate and add the date of initial/index MI or Stroke to the form where fatal MI or fatal stroke is determined.

Additionally, the CEC will work to ensure that any deaths which are not adjudicated as cardiovascular death due to MI or stroke will be reviewed to confirm if they meet the criteria for non-fatal MIs or non-fatal strokes.

- A. Death – All Cause for CV vs. Non-CV Causality
- B. Non-fatal MI
- C. Non-fatal Stroke
- D. Hospitalization for Unstable Angina
- E. Coronary Revascularization – Elective/Urgent
- F. Heart Failure

Death:

I. Cardiovascular Death

Cardiovascular death includes death resulting from: an acute MI, sudden cardiac death, death due to heart failure (HF), death due to stroke, death due to cardiovascular (CV) procedures, death due to CV hemorrhage, and death due to other CV causes.

CV mortality will be classified more specifically (MI, sudden cardiac death, etc.) as follows:

- a. **Death due to Acute Myocardial Infarction** refers to a death by any cardiovascular mechanism (e.g., arrhythmia, sudden death, HF, stroke, pulmonary embolus, peripheral arterial disease) ≤ 30 days¹ after a MI related to the immediate consequences of the MI, such as progressive HF or recalcitrant arrhythmia. We note that there may be assessable mechanisms of cardiovascular death during this time period, but for simplicity if the cardiovascular death occurs ≤ 30 days of the myocardial infarction, it will be considered a death due to myocardial infarction.

Acute MI should be verified to the extent possible by the diagnostic criteria outlined for acute MI in this document or by autopsy findings showing recent MI or recent coronary thrombosis.

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 an elective coronary procedure to treat myocardial ischemia (i.e., chronic stable angina) or death due to a MI that occurs as a direct consequence of a CV investigation/procedure/operation should be considered as death due to a CV procedure

2. **Sudden Cardiac Death** refers to death that occurs unexpectedly, not following an acute MI, and includes the following deaths:
 - a. Death witnessed and occurring 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 electrocardiographic (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 specific cardiac or non-cardiac etiology
 - f. Unwitnessed death in a subject seen alive and clinically stable ≤ 24 hours prior to being found dead without any evidence supporting a specific non-cardiovascular cause of death (information regarding the patient's clinical status preceding death should be provided, if available)

General Considerations

- Unless additional information suggests an alternate specific cause of death (e.g., Death due to Other Cardiovascular Causes), if a patient is seen alive ≤ 24 hours of being found dead, sudden cardiac death (criterion 2f, above) should be recorded. For patients who were not observed alive within 24 hours of death, undetermined cause of death (see section III below) should be recorded (e.g., a subject found dead in bed, but who had not been seen by family for several days).
3. **Death due to Heart Failure** refers to death in association with clinically worsening symptoms and/or signs of heart failure regardless of HF etiology. Deaths due to heart failure can have various etiologies, including single or recurrent myocardial infarctions, ischemic or non-ischemic cardiomyopathy, hypertension, or valvular disease.
 4. **Death due to Stroke** refers to death after a stroke that is either a direct consequence of the stroke or a complication of the stroke. Acute stroke should be verified to the extent possible by the diagnostic criteria outlined for stroke.
 5. **Death due to Cardiovascular Procedures** refers to death caused by the immediate complications of a cardiac procedure.

6. **Death due to Cardiovascular Hemorrhage** refers to death related to hemorrhage such as a non-stroke intracranial hemorrhage, non-procedural or non-traumatic vascular rupture (e.g., aortic aneurysm), or hemorrhage causing cardiac tamponade.
7. **Death due to Other Cardiovascular Causes** refers to a CV death not included in the above categories but with a specific, known cause (e.g., pulmonary embolism or peripheral arterial disease)

II. Non-Cardiovascular Death

Non-cardiovascular death is defined as any death with a specific cause not thought to be CV in nature, as described above (section I). The following is a suggested list of non-CV causes of death:

- Pulmonary
- Renal
- Gastrointestinal
- Hepatobiliary
- Pancreatic
- Infection (includes sepsis)
- Inflammatory (e.g., systemic inflammatory response syndrome [SIRS]/ immune [including autoimmune])
- Hemorrhage that is neither cardiovascular bleeding nor a stroke
- Non-CV procedure or surgery
- Trauma
- Suicide
- Non-prescription drug reaction or overdose
- Prescription Drug Reaction or overdose
- Neurological (non-CV)
- Malignancy
- Other non-CV

Undetermined Cause of Death

Undetermined Cause of Death refers to a death not attributable to one of the above categories of CV death or to a non-CV 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.

Non-fatal Myocardial Infarction:

1. General Considerations

The term myocardial infarction (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 post-mortem pathological finding); and
- Supporting information derived from the clinical presentation, electrocardiographic changes, or the results of myocardial or coronary artery imaging

The totality of the clinical, electrocardiographic, and cardiac biomarker information should be considered to determine whether or not a MI has occurred. Specifically, timing and trends in cardiac biomarkers and electrocardiographic 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 electrocardiographic results are not available.

2. Criteria for Myocardial Infarction

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 that are associated with elevations in cardiac biomarkers (e.g., trauma, surgery, pacing, ablation, congestive heart failure, 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 upper reference limit (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. **In general, troponins are preferred. CK-MB should be used if troponins are not available, and total CK may be used in the absence of CK-MB and troponin.**

For MI subtypes (see below), different biomarker elevations for CK, CK-MB, or troponin will be required. The specific criteria will be referenced to the URL.

In many studies, particularly those in which patients present acutely to hospitals which 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 inter-assay variability.

Since the prognostic significance of different types of myocardial infarctions (e.g., peri-procedural myocardial infarction versus spontaneous myocardial infarction) may be different, consider evaluating outcomes for these subsets of patients separately.

c. Electrocardiogram (ECG) changes

Electrocardiogram changes can be used to support or confirm a MI.

Supporting evidence may be ischemic changes and confirmatory information may be new Q waves.

- ECG manifestations of acute myocardial ischemia (in absence of left ventricular hypertrophy (LVH) and left bundle branch block (LBBB)):
 - ST elevation: New ST elevation at the J point in two contiguous leads with the cut-points: ≥ 0.1 mV in all leads other than leads V2-V3 where the following cut-points apply: ≥ 0.2 mV in men ≥ 40 years (≥ 0.25 mV in men < 40 years) or ≥ 0.15 mV in women.
 - ST depression and T-wave changes: New horizontal or down-sloping ST depression ≥ 0.05 mV in two contiguous leads and/or new T inversion ≥ 0.1 mV in two contiguous leads with prominent R wave or R/S ratio > 1 .

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 ≥ 0.01 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; V1-V6; II, III, and aVF)^a

The same criteria are used for supplemental leads V7-V9, and for the Cabrera frontal plane lead grouping.

- ECG changes associated with prior myocardial infarction
 - 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
- Criteria for prior myocardial infarction
Any one of the following criteria meets the diagnosis for prior MI:
 - Pathological Q waves with or without symptoms in the absence of non-ischemic causes
 - Imaging evidence of a region of loss of viable myocardium that is thinned and fails to contract, in the absence of non-ischemic cause
 - Pathological findings of a prior myocardial infarction

MI Subtypes:

For each MI identified by the CEC, a Type of MI will be assigned using the following guidelines:

- **Type 1 Spontaneous MI**
Spontaneous MI related to atherosclerotic plaque rupture, ulceration, fissuring, erosion, or dissection with resulting intraluminal thrombus in one or more of the coronary arteries leading to decreased myocardial blood flow or distal platelet emboli with ensuing myocyte necrosis. The patient may have underlying severe CAD but on occasion non-obstructive or no CAD may be found at angiography, particularly in women.
- **Type 2 Myocardial Infarction secondary to an ischemic imbalance**
In instances of myocardial injury with necrosis where a condition OTHER THAN CAD contributes to an imbalance between myocardial oxygen supply and/or demand, (e.g., coronary endothelial dysfunction, coronary artery spasm, coronary embolism, tachy-/brady-arrhythmias, anemia, respiratory failure, hypotension, and hypertension with or without left ventricular hypertrophy). In critically ill patients, or in patients undergoing major (non-cardiac) surgery, elevated values of cardiac biomarkers may appear, due to the direct toxic effects of endogenous or exogenous high circulating catecholamine levels. Also coronary vasospasm and/or endothelial dysfunction have the potential to cause MI.
- **Type 3 Myocardial infarction resulting in death when biomarker values are unavailable**
Cardiac death with symptoms suggestive of myocardial ischemia and presumed new ischemic ECG changes or new LBBB, but death occurring before blood samples could be obtained, before cardiac biomarker values could increase, or in rare cases were not collected.
- **Type 4a Myocardial infarction related to percutaneous coronary intervention (PCI)**
Percutaneous coronary intervention (PCI) related MI is arbitrarily defined by elevation of cTn values (>5 x 99th percentile URL) in patients with normal baseline values (\leq 99th percentile URL) or a rise of cTn values $>20\%$ if the baseline values are elevated and are stable or falling. In addition, either (i) symptoms suggestive of myocardial ischemia, or (ii) new ischemic ECG changes or new LBBB, or (iii) angiographic loss of patency of a major coronary artery or a side branch or persistent slow or no-flow embolization, or (iv) imaging

demonstration of new loss of viable myocardium or new regional wall motion abnormality are required.

- **Type 4b Myocardial Infarction related to stent thrombosis**
Myocardial infarction associated with stent thrombosis is detected by coronary angiography or autopsy in the setting of myocardial ischemia and with a rise and/or fall of cardiac biomarkers values with at least one value above the 99th percentile URL.
- **Type 4c Myocardial Infarction related to PCI restenosis**
Myocardial infarction related to PCI restenosis is defined as $\geq 50\%$ stenosis at coronary angiography or a complex lesion associated with a rise and/or fall of cTn values > 99 th percentile URL and no other significant obstructive coronary artery disease (CAD) of greater severity following: (i) initially successful stent deployment, or (ii) dilation of a coronary artery stenosis with balloon angioplasty ($< 50\%$).
- **Type 5 Myocardial Infarction related to coronary artery bypass grafting (CABG)**
Myocardial infarction associated with CABG is arbitrarily defined by elevation of cardiac biomarker values ($> 10 \times$ 99th percentile URL) in patients with normal baseline cTn values (\leq 99th percentile URL) plus, either (i) new pathological Q waves or new LBBB, or (ii) angiographic documented new graft or new native coronary artery occlusion, or (iii) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.

Non-fatal Stroke and TIA

STROKE VS. TRANSIENT ISCHEMIC ATTACK (TIA):

The distinction between a TIA and an Ischemic Stroke is the presence of infarction. Persistence of symptoms is an acceptable indicator of acute infarction.

TIA

TIA is described as a transient episode of focal neurological dysfunction caused by brain, spinal cord, or retinal ischemia, *without acute infarction*.

Note: Subdural hematomas and epidural bleeds are intracranial hemorrhagic events and NOT strokes.

STROKE

Stroke is defined as an acute episode of focal or global neurological dysfunction, generally lasting more than 24 hours, caused by brain, spinal cord, or retinal injury as a result of hemorrhage or infarction. For each stroke identified by the CEC, the event will be further categorized using the following guidelines:

A. Ischemic Stroke

Ischemic stroke is defined as an acute episode of focal cerebral, spinal, or retinal dysfunction caused by 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 intraparenchymal, intraventricular, or subarachnoid hemorrhage.

C. Undetermined Stroke

Undetermined stroke is defined as an acute episode of focal or global neurological dysfunction caused by presumed brain, spinal cord, or retinal vascular injury as a result of hemorrhage or infarction but with insufficient information to allow categorization as A or B.

Hospitalization for Unstable Angina:

Hospitalization for Unstable Angina is defined as:

1. Ischemic discomfort (*angina or symptoms thought to be equivalent*) > 10 minutes in duration occurring:

- At rest, *or*
- In an increasing pattern with frequent episodes associated with progressively decreased exercise capacity.

AND

2. Prompting an unscheduled hospitalization **within 24 hours** of the most recent symptoms. Hospitalization is 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 change in calendar date if the hospital admission or discharge times are not available).

AND

3. At least 1 of the following:

a. New or worsening ST or T wave changes on resting ECG (in the absence of confounders such as LVH and LBBB)

- Transient ST elevation (duration < 20 minutes)

New ST elevation at the J point in two contiguous leads with the cut-points: ≥ 0.1 mV in all leads other than leads V2-V3 where the following cut-points apply: ≥ 0.2 mV in men ≥ 40 years (≥ 0.25 mV in men < 40 years) or ≥ 0.15 mV in women.

- 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 ≥ 0.3 mV in 2 contiguous leads with prominent R wave or R/S ratio >1 .

- b. Definite evidence of inducible myocardial ischemia as demonstrated by:
- An early positive exercise stress test, defined as ST elevation or ≥ 2 mm ST depression prior to 5 mets **OR**
 - stress echocardiography (reversible wall motion abnormality) **OR**
 - myocardial scintigraphy (reversible perfusion defect), **OR**
 - MRI (myocardial perfusion deficit under pharmacologic stress).

AND believed to be responsible for the myocardial ischemic symptoms/signs.

- c. Angiographic evidence of new or worse $\geq 70\%$ lesion and/or thrombus in an epicardial coronary artery that is believed to be responsible for the myocardial ischemic symptoms/signs.
- d. Need for coronary revascularization procedure (PCI or CABG) for the presumed culprit lesion(s). This criterion would be fulfilled if revascularization was undertaken during the unscheduled hospitalization, or subsequent to transfer to another institution without interceding home discharge.

AND

4. Negative cardiac biomarkers and no evidence of acute MI.

General Considerations

1. Escalation of pharmacotherapy for ischemia, such as IV nitrates or increasing doses of β -blockers, should be considered supportive but not diagnostic of the diagnosis of unstable angina. However, a typical presentation and admission to the hospital with escalation of pharmacotherapy, without any of the additional findings listed under category 3 (above), would be insufficient to support classification as hospitalization for unstable angina.
2. If subjects are admitted with suspected unstable angina, and subsequent testing reveals a non-cardiac or non-ischemic etiology, this event should not be recorded as hospitalization for unstable angina. Potential ischemic events meeting the criteria for myocardial infarction should not be adjudicated as unstable angina.
3. Planned hospitalization or rehospitalization for performance of an elective revascularization in patients who do not fulfill the criteria for unstable angina should not be considered a hospitalization for unstable angina. For example,
 - Hospitalization of a patient with stable exertional angina for coronary angiography and PCI that is prompted by a positive outpatient stress test should not be considered hospitalization for unstable angina.

- Rehospitalization of a patient meeting the criteria for unstable angina who was stabilized, discharged, and subsequently readmitted for revascularization, does not constitute a second hospitalization for unstable angina.
4. A patient who undergoes an elective catheterization where incidental coronary artery disease is found and who subsequently undergoes coronary revascularization will not be considered as meeting the hospitalization for unstable angina end point.
 5. A patient who has UA and subsequently dies should be adjudicated as defined above (see Section I) to determined cause of death.

Cardiac Revascularization Procedure:

CORONARY REVASCULARIZATION

A cardiac (coronary) revascularization procedure is defined as either coronary artery bypass graft surgery (CABG) or a percutaneous coronary intervention (PCI) (e.g., angioplasty, coronary stenting). CABG is defined as the successful placement of at least one conduit with either a proximal and distal anastomosis or a distal anastomosis only. PCI is defined as placement of an angioplasty guidewire, balloon, or other device (e.g., stent, atherectomy catheter brachytherapy delivery device, or thrombectomy catheter) into a native coronary artery or coronary artery bypass graft for the purpose of mechanical coronary revascularization. In the assessment of the severity of coronary lesions with the use of intravascular ultrasound, CFR, or FFR, insertion of a guide wire will NOT be considered PCI. Coronary Artery Bypass Graft surgeries and Percutaneous Coronary Interventions will be categorized into two distinct categories, elective and urgent:

a. Elective

The procedure can be performed on an outpatient basis or during a subsequent hospitalization without significant risk of myocardial infarction (MI) or death. For stable inpatients, the procedure is being performed during this hospitalization for convenience and ease of scheduling and NOT because the patient's clinical situation demands the procedure prior to discharge.

b. Non-Elective

Non Elective procedures will include the following:

Urgent: The procedure should be performed on an inpatient basis and prior to discharge because of significant concerns that there is risk of myocardial ischemia, MI, and/or death. Patients who are outpatients or in the emergency department at the time that the cardiac catheterization is requested would warrant hospital admission based on their clinical presentation.

Emergent: The procedure should be performed as soon as possible because of substantial concerns that ongoing myocardial ischemia and/or MI could lead to death. "As soon as possible" refers to a patient who is of sufficient acuity that one would cancel a scheduled case to perform this procedure immediately in the next available room during business hours, or one would activate the on-call team were this to occur during off-hours.

Salvage: The procedure is a last resort. The patient is in cardiogenic shock when the PCI begins (i.e., the time at which the first guide wire or intracoronary device is introduced into a coronary artery or bypass graft for the purpose of mechanical revascularization) OR within the last ten minutes prior to the start of the case or during the diagnostic portion of the case, the patient has also received chest compressions or has been on unanticipated circulatory support (e.g., intra-aortic balloon pump, extracorporeal mechanical oxygenation, or cardiopulmonary support).

Heart Failure:

Heart Failure Event

A **Heart Failure Event** includes hospitalization for heart failure and may include urgent outpatient visits. HF hospitalizations should remain delineated from urgent visits. If urgent visits are included in the HF event endpoint, the number of urgent visits needs to be explicitly presented separately from the hospitalizations.

A **Heart Failure Hospitalization** is defined as an event that meets ALL of the following criteria:

- 1) The patient is admitted to the hospital with a primary diagnosis of HF
- 2) The patient's length-of-stay in hospital extends for at least 24 hours (or a change in the calendar date if the hospital admission and discharge times are unavailable)
- 3) The patient exhibits documented new or worsening symptoms due to HF on presentation, including at least ONE of the following:
 - a. Dyspnea (dyspnea with exertion, dyspnea at rest, orthopnea, paroxysmal nocturnal dyspnea)
 - b. Decreased exercise tolerance
 - c. Fatigue
- 4) The patient has objective evidence of new or worsening HF, consisting of at least TWO physical examination findings OR one physical examination finding and at least ONE laboratory criterion), including:
 - a. Physical examination findings considered to be due to heart failure, including new or worsened:
 - i. Peripheral edema
 - ii. Increasing abdominal distention or ascites (in absence of primary hepatic disease)
 - iii. Pulmonary rales/crackles/crepitations
 - iv. Increased jugular venous pressure and/or hepatojugular reflux
 - v. S₃ gallop
 - vi. Clinically significant or rapid weight gain thought to be related to fluid retention

b. Laboratory evidence of new or worsening HF, if obtained within 24 hours of presentation, including:

- i. Increased B-type natriuretic peptide (BNP)/ N-terminal pro-BNP (NT-proBNP) concentrations consistent with decompensation of heart failure (such as BNP >500 pg/mL or NT-proBNP >2,000 pg/mL). In patients with chronically elevated natriuretic peptides, a significant increase should be noted above baseline.
- ii. Radiological evidence of pulmonary congestion
- iii. Non-Invasive diagnostic evidence of clinically significant elevated left- or right-sided ventricular filling pressure or low cardiac output. For example, echocardiographic criteria could include: E/e' >15 or D-dominant pulmonary venous inflow pattern, plethoric inferior vena cava with minimal collapse on inspiration, or decreased left ventricular outflow (LVOT) minute stroke distance (time velocity integral (TVI))

OR

- iv. Invasive diagnostic evidence with right heart catheterization showing a pulmonary capillary wedge pressure (pulmonary artery occlusion pressure) ≥ 18 mmHg, central venous pressure ≥ 12 mmHg, or a cardiac index < 2.2 L/min/m²

Note: All results from diagnostic tests should be reported, if available, even if they do not meet the above criteria, because they provide important information for the adjudication of these events.

5) The patient receives initiation of intensification of treatment specifically for HF, including **at least ONE** of the following:

- a. Augmentation in oral diuretic therapy
- b. Intravenous diuretic, inotrope, or vasodilator therapy
- c. Mechanical or surgical intervention, including:
 - i. Mechanical circulatory support (e.g., intra-aortic balloon pump, ventricular assist device)
 - ii. Mechanical fluid removal (e.g. ultrafiltration, hemofiltration, dialysis)

An **Urgent Heart Failure Visit** is defined as an event that meets all of the following:

- 1) The patient has an urgent, unscheduled office/practice or emergency department visit for a primary diagnosis of HF, but not meeting the criteria for a HF hospitalization
- 2) All signs and symptoms for HF hospitalization (i.e., 3) symptoms, 4) physical examination findings, and 5) laboratory evidence of new or worsening HF, as indicated above) must be met.
- 3) The patient receives initiation or intensification of treatment specifically for HF, as detailed in the above section with the exception of oral diuretic therapy, which will not be sufficient.