

# Low Prognostic Value of Novel Nocturnal Metrics in Patients With OSA and High Cardiovascular Event Risk

## Post Hoc Analyses of the SAVE Study

*Dominik Linz, MD, PhD; Kelly A. Loffler, PhD; Prashanthan Sanders, PhD; Peter Catchside, PhD; Craig S. Anderson, MD, PhD; Danni Zheng, PhD; WeiWei Quan, MD, PhD; Mary Barnes, BSc (Hons), GDipMath; Susan Redline, MD, MPH; R. Doug McEvoy, MD; and Mathias Baumert, PhD; on behalf of the SAVE (Sleep Apnea Cardiovascular Endpoints) Investigators*

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## **e-Appendix 1.**

### **SAVE STUDY GROUP AND SITE INVESTIGATORS**

#### **Executive Committee**

R. Doug McEvoy (Chair, Principal Investigator), Adelaide Institute for Sleep Health, Flinders University, Adelaide, Australia

Craig Anderson (Co-Chair, Co-Principal Investigator), The George Institute for Global Health, University of Sydney and Royal Prince Alfred Hospital, Sydney, Australia; The George Institute, China, Beijing, China

Ron Grunstein, Woolcock Institute of Medical Research, University of Sydney, Sydney, Australia

Jan Hedner, Department of Internal Medicine, Sahlgrenska University Hospital, Gothenburg, Sweden

Shaoguang Huang, Sleep Disorders Department, Ruijin Hospital, Shanghai Jiao Tong University, Shanghai, China

Geraldo Lorenzi-Filho, Heart Institute, Instituto do Coracao (InCor), University of Sao Paulo, Sao Paulo, Brazil

Bruce Neal, The George Institute for Global Health, University of Sydney, Sydney, Australia Lyle Palmer, School of Public Health, University of Adelaide, Adelaide, Australia

Susan Redline, Sleep Medicine - Harvard Medical School, Brigham and Women's Hospital and Beth Israel Deaconess Medical Center, Boston, United States

Jiguang Wang, Shanghai Institute for Hypertension, Ruijin Hospital and Shanghai Jiaotong University, Shanghai, China

Nanshan Zhong, The First Affiliated Hospital of Guangzhou Medical University, State Key Laboratory of Respiratory Disease, Guangzhou, China

#### **Operations Committee**

R. Doug McEvoy and Nick Antic, Adelaide Institute for Sleep Health, Flinders University, Adelaide, Australia; Craig Anderson, Emma Heeley, Ruth Freed, Tina Cheung, Natalie Espinosa, Sarah Leighton, Tara Sassé, Kim Bailey, Swamy Chintapatla, Al Freeman, Bryan Holder, Adele Hosseini, Michelle Leroux, Hugh Senior, Georgena Thomopoulos, Robyn Walsh and Zahara Wolfowicz, The George Institute, Australia

#### **Data Safety Monitoring Board**

Garry Jennings (Chair), National Heart Foundation of Australia, Melbourne, Australia Guy Marks, Woolcock Institute of Medical Research and University of New South Wales, Sydney, Australia

K.S. Lawrence Wong, Department of Medicine and Therapeutics, Chinese University of Hong Kong, Hong Kong, China

#### **Statisticians**

Laurent Billot, Qiang Li, Jayanthi Mysore, Sandrine Stepien and Stephane Heritier, The George Institute for Global Health, Australia Independent Sleep Expert (China)

Xiheng Guo, Beijing Chao Yang Hospital

#### **Endpoint Adjudicators**

Yongjun Cao, Second Affiliated Hospital of Soochow University, China

Carlos Campos, University of Sao Paulo, Instituto do Coracao (InCor), Sao Paulo, Brazil Candice Delcourt, The George Institute for Global Health, University of Sydney and Royal Prince Alfred Hospital, Sydney, Australia

Glaucylara Geovanini, Heart Institute, Instituto do Coracao (InCor), University of Sao Paulo, Sao Paulo, Brazil, Brigham and Women's Hospital, Boston, United States

Dennis Lau, Royal Adelaide Hospital and The University of Adelaide, Adelaide, Australia Alejandra Malavera, The George Institute for Global Health, Australia

Eng Lee Ooi, The University of Adelaide, The Queen Elizabeth Hospital, Lyell McEwin Hospital, Adelaide, Australia

Karla Santo, The George Institute for Global Health, Australia

Lili Song, Department of Neurology, 85 Hospital of People's Liberation Army, China Weiwei Quan, Cardiovascular Department Ruijin Hospital affiliated to Shanghai Jiaotong University School of Medicine, China

Min-Xia Wang, Royal Prince Alfred Hospital, University of Sydney, Australia Guojun Wu, Neurology Department, Hebei Province Yutian County Hospital, China

Jie Yang, Neurology Department, Nanjing First Hospital, Nanjing Medical University, Nanjing, China

Hooishan Yap, Flinders Medical Centre, Adelaide, Australia

Shihong Zhang, Neurology Department, West China Hospital, Sichuan University, China

### **International Coordinating Center (ICC) - The George Institute for Global Health, Australia**

*Project Management & Operations* – Emma Heeley (Study Director), Ruth Freed (Project Manager), Tina Cheung, Natalie Espinosa, Sarah Leighton, Tara Sassé, Kim Bailey, Swamy Chintapatla, Al Freeman, Bryan Holder, Adele Hosseini, Michelle Leroux, Hugh Senior, Georgena Thomopoulos, Robyn Walsh and Zahava Wolfowicz; *Data Management and Programming* – Manuela Armenis, Dominic Byrne, Paul Donnelly, Mirza Ahmad Baig and Nick Blacklock; *Contracts and Quality Assurance* – Helen Monaghan, Phillipa Smith, Parisa Glass, Magdalen Malone, Marna Van Zyl, Carolyn Rodger.

### **Strategic Study Management Center (SMC) – Adelaide Institute for Sleep Health, Adelaide, Australia**

*CoreLab* – Nick Antic, Laura Bandick, Michaela O'Keefe, Amanda McKenna, Jeremy Mercer, Mark Jurisevic, Samantha Mead; *Business and Finance* – Adrian Klauber, Leanne Cox.

### **Regional Coordinating Centers (RCCs)**

Australia (Adelaide Institute for Sleep Health) – Denzil Paul; Brazil (CR Pesquisa Clínica) – Sergio Tutya (Project Manager), Alessandro Betito, Diogo Moia; (Medicamenta MRS) – Joyce Marinho, Lara Cavalcante; China (The George Institute China incorporating George Clinical) – Shu Ying (Project Manager), Yuehan Zheng, Wei Wei, Hongyu Zhang, Jing Zhou, Haijing Jia, Meng Zhaung, Xiaoying Chen, Buliang Cui, Hua Deng, Xiaofen Ding, Nan Li, Hui Lin, Bochen Liu, Aiwu Song, Jian Sun, Sai Nan Wang, Feifei Zhao, Ying Zhuang; India (The George Institute India incorporating George Clinical) – Hemalata Boyini (Project Manager), Mallikarjuna Kunigari; Spain (Hospital Universitario de Guadalajara, supported by Spanish Respiratory Society (SEPAR) and the Fondo de Investigaciones Sanitarias (FIS)) – Olga Mediano (Project Manager), Esther Viejo, Nieves Mayoral, Javier Rubio.

### **SAVE Principal Investigators, Co-Investigators and Coordinators (according to country and center)**

**Australia** – *Sir Charles Gairdner Hospital*: S. Mukherjee, N. McArdle, B.M. Boeing, L. Palmer, D. Hillman, S.C. Rea; *Repatriation General Hospital*: R. D. McEvoy,

N. Antic, D. Paul, A. McKenna; *Royal Prince Alfred Hospital*: C.A. Anderson, C. Delcourt, C. Carcel, E. Ray, T. Paraskevaidis, S. Small, J. Levitt; *The Prince Charles Hospital*: J. Douglas, N. Dunn, D. Walters, L. Lan, J. Mikli, A. Wong, D. Curtin, J. Robinson; *Lyell McEwin Hospital*: M. Arstall, N. Lamberts, W. Jeffries; *Box Hill Hospital (ECRU)*: A.C. Young, I. Shinkarkasy, I. Shinkarkasy, F. Thien, D. O'Driscoll, A. Anniss, S. Dal Sasso; *Flinders Medical Centre*: D.P. Chew, F. Wollaston, K. Luscombe; *Alfred Hospital – CCRC Clinical Trial Centre*: M. Naughton, M. Hooy, S. Yorkston; *Royal Melbourne Hospital*: J. Goldin, J. Eritaia, E. White, A. Perkins; *University of Adelaide, Cardiovascular Centre*: P. Sanders, R. Sharp, K. Milburn; *Monash Medical Centre*: G. Hamilton, J. McKenzie; *Concord Hospital*: A. Corbett, R. Portley.

**Brazil** – *Instituto do Coração – INCOR*: G. Lorenzi-Filho, L. Drager, G.A. Souza,

D.B.C. Queiróz; *Pronto Socorro Cardiológico de Pernambuco*: R.P. Pedrosa, A. Medeiros, M. Carvalho, B. Thais Clementino; *Instituto Dante Pazzanese de Cardiologia*:

C. Amodeo, J. Silva, R. Depizzol, D. de Andrade, A. Bertolami, C. Gonzaga; *Instituto do Sono / AFIP*: L. Bittencourt, C. Ferreira, M. Bignotto; *Clínica de Pneumologia e Medicina do Sono (12)*: A. Petruco; *Hospital Universitário - Universidade de São Paulo*:

L.F. Drager; *Hospital Beneficência Portuguesa*: P.R. Genta; *Labsono - Diagnostico e Solucoes em Sono*: S. Fagondes, C. Perin.

**China** – *The First Affiliated Hospital of Guangzhou Medical University*: Y. Luo, Z. Qiu; *Guangdong General Hospital*: Q. Ou; *The First Affiliated Hospital of Nanjing Medical University*: X. Zhang; *The Second Affiliated Hospital of Soochow University*: R. Chen, Y. Sun, Y. He; *Fuwai Hospital*: Z. Liu, Z. Zhao, Q. Luo, Q. Zhao; *Xuzhou Central Hospital*: G. Chen; *Hejian Municipal People's Hospital*: B. Du, Y. Wang, Y. Guo, W. Dong, L. Wu, K. Yu, S. Wang, J. Shi; *Jiangsu Provincial Hospital of State Organ*: Z. Pan, Y. Dou, M. Zhu; *Beijing Shougang Hospital*: W. Gao; *The Second Affiliated Hospital of Hebei Medical University*: L. Tai, H. Wang; *Jiangsu Provincial Hospital Of State Organ*: G. Lu; *Baotou Central Hospital*: Y. Li, X. Li, R. Pan, H. Xue; *The Third Hospital of Hebei Medical University*: H. Wang; *Peking Union Medical College Hospital*: Y. Xiao, R. Huang; *The Second Affiliated Hospital of Guangzhou Medical College*: E. Xu, Q. Lin; *Guangxi People's Hospital of Guangxi Zhuang Autonomous Region*: J. Liu; *Zhongshan Hospital Fudan University*: S. Li, W. Li, X. Wu, J. Zhou, H. Jiang; *General Hospital of Tianjin Medical University*: B. Chen, Y. Ma; *Xinhua Hospital*: X. Guo, L. Ren, J. Sun, Y. Sun; *First Affiliated Hospital of Chinese Medical University*: W. Wang, H. Shen; *The First People's Hospital of Foshan*: G. Zhen; *Beijing Shijitan Hospital (Neurology Department)*: M. He, J. Liu; *The Second Hospital of Shanxi Medical University*: B. Wang, Z. Liu, H. Zhao, X. Gao,

Y. Fan; *The First Affiliated Hospital of Baotou Medical College*: L. Wu, X. Guo, J. Wu;

*Shanghai Huadong Hospital*: H. Zhu; *Beijing Haidian Hospital*: F. Yu, X. Meng,

W. Liu, X. Chen, X. Tang; *Shanghai Shidong Hospital*: X. Liu, M. Wang; *Shanghai Pulmonary Hospital*: Y. Liang; *The Fifth Affiliated Hospital, Sun Yat-Sen University*: Z. Li, X. Xu; *Beijing Tongren Hospital - Department of Neurology*: X. Zhang; *Beijing Shijitan Hospital (Sleep Monitoring Centre)*: L. Pan, X. Ma; *Zhejiang Hospital*: G. Qin; *The First Affiliated Hospital of Shanxi Medical University*: S. Ren; *No. 260 PLA Hospital of China*: S. Tian, J. Zhang; *Beijing Friendship Hospital, Capital Medical University*: K. Chen; *Beijing Police Hospital*: G. Xiao; *Ji Shui Tan Hospital (Cardiology Department)*: X. Zhao, Z. Ma; *Sino-Japan Friendship Hospital*: J. Lin, Y. Li; *Shanghai Ruijin Hospital*: M. Li; *Zengcheng People's Hospital*: R. Zou, H. Zhang, J. Guo; *The First People's Hospital of Changzhou*: C. Li, W. Peng; *301 Hospital Cardiology Department*: L. Gai; *Nanjing Jiangning Hospital*: X. Zhang; *The First People's Hospital of Wujiang*: Q. Wu, X. Lu; *Peking University First Hospital*: Y. Huang; *Tai Yuan City Centre Hospital*: P. Wang; *Beijing Tongren Hospital*: L. Li.

**India** - *All India Institute of Medical Sciences (AIIMS)*: M. Tripathi, P. Madakasira, S. Sharma, R. Verma; *BYL Nair Hospital*: J.M. Joshi, V. Karkhanis, S. Jaguste, M. Shah, S. Kalamkar, S. Kulkarni; *Christian Medical College Hospital, Ludhiana*: J.D. Pandian, N. Akhtar, D. Sharma; *Global Hospital*: M. Samiuddin; *Vijaya Health Center*: S. Kumar, M. Esunathan; *PSG Hospital*: R.M.P.L. Ramanathan, C. Subramaniamim, F. V. Jeyanthi; *King Edward Memorial (KEM) Hospital, Mumbai*: P. Kerkar, C. Lanjewar, R. Sharma, L. Desai; *Mediciti Hospital*: A. Bordoloi, N.C.R. Podduturi, S.R. Savusani; *Chest Clinic, Sri Ramakrishna Medical Centre*: M.K. Thekkinkattil, S. Muthuvairu.

**New Zealand** – *Christchurch Hospital*: M.C. Hlavac, M.J. Epton, M.K. Storer,

J.M. Cook; *Dunedin Hospital*: B. Brockway, J. Cowan, D.R. Taylor, E. Cox, R. Palmay; *Hutt Valley District Health Board*: K. Ferrier, J. Dewar, R. Kleintjes, J. Kovacs, A. Campbell, A. Neill; *Waikato Hospital*: C.L. Chang, C. Tuffery, S. Hopping, J. McLachlan; *Tauranga Hospital*: A.N. Graham, M.E. Molloy.

**Spain** – *Hospital Universitario de Guadalajara*: O. Mediano, M.I. Valiente-Díaz, N. Mayoral, J. Rubio, M.E. Viejo-Ayuso, J.M. Román-Sánchez, C. Rodriguez-García, J. Balaguer; *Hospital Sabadell Corporació Parc Tauli*: M.J. Masdeu, M. Piñar, L. Vigil, D. Gonzalez, G. Sansa, D. Canovas; *Hospital Doce de Octubre*: M.J. Diaz de Atauri, T. Diaz-Cambriles, P.D. Benavides-Manas, A. Hernando-Sanz, A. Candel-Pizarro, R. Chorro- Fito, E.M. Arias, J. Munoz Mendez; *Hospital Arnau de Vilanova*: F. Barbé Illa, S. Gomez Falguera, O. Minguez, L. Pascual; *Hospital Txagorritxu*: J. Durán, C. Egea Santaolalla.

**United States** – *Mayo Clinic*: S. Caples, N. Slocumb

**e-Table 1:** SAVE sites and ethics approval details

Site Name	Country	IRB/EC Name	Project Approval Number/Application Number
LYELL MCEWIN HOSPITAL	Australia	Central Northern Adelaide Health Service, Ethics of Human Research Committee (TQEH & LMH)	2008114
FLINDERS MEDICAL CENTRE	Australia	Southern Adelaide Clinical Human Research Ethics Committee	200.08
CAULFIELD CLINICAL TRIALS CENTRE	Australia	Alfred Hospital Ethics Committee	289/08
ROYAL PRINCE ALFRED HOSPITAL	Australia	Sydney South West Area Health Service (SSWAHS) HREC - CRGH	CH52/6/2008 - 08/CRGH/126
CONCORD REPATRIATION GENERAL HOSPITAL	Australia	Sydney South West Area Health Service (SSWAHS) HREC - CRGH	CH52/6/2008 - 08/CRGH/126
ECRU (BOX HILL HOSPITAL)	Australia	Eastern Health Human Research Ethics Committee	E27/0809
ROYAL MELBOURNE HOSPITAL	Australia	Melbourne Health HREC	2008.207
THE PRINCE CHARLES HOSPITAL	Australia	Human Research and Ethics Committee, The Prince Charles Hospital	EC28123
WASDRI (SIR CHARLES GAIRDNER HOSPITAL)	Australia	Sir Charles Gairdner Hospital Human Research Ethics Committee	2008-167
REPATRIATION GENERAL HOSPITAL	Australia	Southern Adelaide Clinical Human Research Ethics Committee	200.08
MONASH MEDICAL CENTRE	Australia	Monash Health Human Research Ethics Committee	09005A
CARDIOVASCULAR CENTRE ADELAIDE	Australia	Royal Adelaide Hospital Research Ethics Committee	101215a
WAIKATO HOSPITAL	New Zealand	The Southern Health and Disability Ethics Committees	MEC/09/08/087
HUTT HOSPITAL	New Zealand	Multi-region Ethics Committee	MEC/09/08/087
DUNEDIN HOSPITAL	New Zealand	Multi-region Ethics Committee	MEC/09/08/087
CHRISTCHURCH HOSPITAL	New Zealand	Multi-region Ethics Committee	MEC/09/08/087
TAURANGA HOSPITAL	New Zealand	Multi-region Ethics Committee	MEC/09/08/087
LABSONO - DIAGNOSTICO E SOLUCOES EM SONO	Brazil	HCPA – HOSPITAL DE CLÍNICAS DE PORTO ALEGRE, Comissão Científica e Comissão de Pesquisa e ética em saúde	110266



PRONTO SOCORRO CARDIOLOGICO DE PERNAMBUCO	Brazil	COMITÊ DE ÉTICA EM PESQUISA EM SERES HUMANOS, COMPLEXO HOSPITALAR HUOC/PROCAPE	395092
CLINICA DE PNEUMOLOGIA E MEDICINA DO SONO	Brazil	COMITÊ PERMANENTE DE ÉTICA EM PESQUISA ENVOLVENDO SERES HUMANOS	0238/11
HOSPITAL BENEFICENCIA PORTUGUESA	Brazil	Beneficência Portuguesa de São Paulo COMITÊ DE ÉTICA EM PESQUISA	729-11
HOSPITAL UNIVERSITARIO - SAO PAULO	Brazil	Research Ethics Committee of Hospital Universitário da USP	1078/10
INSTITUTO DANTE PAZZANESE DE CARDIOLOGIA	Brazil	INSTITUTO DANTE PAZZANESE DE CARDIOLOGIA, Research Ethics Committee	3997
INSTITUTO DO CORACAO (INCOR)	Brazil	HOSPITAL DAS CLÍNICAS DA FMUSP Comissão de Ética para Análise de Projetos de Pesquisa	0666/10
INSTITUTO DO SONO - AFIP	Brazil	Comitê de Ética em Pesquisa da Universidade Federal de São Paulo/ Hospital São Paulo	CEP 0071/11
301 HOSPITAL - DEPARTMENT OF CARDIOLOGY	China	Ethics Committee of Shanghai Ruijin Hospital	(2008) EC REVIEW (34)
BEIJING POLICE HOSPITAL	China	Ethics Committee of Shanghai Ruijin Hospital	(2008) EC REVIEW (34)
BEIJING SHIJITAN HOSPITAL - DEP OF NEUROLOGY	China	Ethics Committee of Shanghai Ruijin Hospital	(2008) EC REVIEW (34)
INNER MONGOLIA BATOU CITY CENTRAL HOSPITAL	China	Ethics Committee of Shanghai Ruijin Hospital	(2008) EC REVIEW (34)
FIRST AFFILIATED HOSPITAL OF CHINESE MED UNI	China	Ethics Committee of First Affiliated Hospital of Chinese Medical University	EC [2008]74
FUWAI HOSPITAL	China	Ethics Committee of Fuwai Hospital	2008-157
GENERAL HOSPITAL OF TIANJIN MEDICAL UNI	China	Ethics Committee of Shanghai Ruijin Hospital	(2008) EC REVIEW (34)
GUANGDONG PROVINCIAL PEOPLES HOSPITAL	China	Ethics Committee of Guangdong Provincial People's Hospital	Yue Yi EC [2008]65-1
JI SHUI TAN HOSPITAL	China	Ethics Committee of Ji Shui Tan Hospital	201110-04
JIANGSU PROVINCIAL HOSPITAL OF STATE ORGAN	China	Ethics Committee of Shanghai Ruijin Hospital	(2008) EC REVIEW (34)
PEKING UNION MEDICAL COLLEGE HOSPITAL - RESP	China	Ethics Committee of Peking Union Medical College Hospital	SAVE
PEKING UNIVERSITY FIRST HOSPITAL	China	Ethics Committee of Peking University First Hospital	[2009]187
SHANGHAI HUADONG HOSPITAL	China	Ethics Committee of Shanghai Ruijin Hospital	(2008) EC REVIEW (34)
SHANGHAI PULMONARY HOSPITAL	China	Ethics Committee of Shanghai Ruijin Hospital	(2008) EC REVIEW (34)





SHANGHAI RUIJIN HOSPITAL	China	Ethics Committee of Shanghai Ruijin Hospital	(2008) EC REVIEW (34)
SINO-JAPAN FRIENDSHIP HOSPITAL	China	Ethics Committee of Sino-Japan Friendship Hospital	2009-29
THE FIFTH AFFILIATED HOSPITAL	China	Ethics Committee of Shanghai Ruijin Hospital	(2008) EC REVIEW (34)
THE FIRST AFFILIATED HOSPITAL OF GUANGZHOU	China	Ethics Committee of The First Affiliated Hospital of Guangzhou Medical College	(2008) EC REVIEW (34)
THE FIRST AFFILIATED HOSPITAL OF NANJING	China	Ethics Committee of The First Affiliated Hospital of Nanjing Medical University	(2008) EC (031316)
THE FIRST PEOPLES HOSPITAL OF CHANGZHOU	China	Ethics Committee of The First People's Hospital of Changzhou	[2009]01
THE SECOND AFFILIATED HOSPITAL OF GUANGZHOU	China	Ethics Committee of Shanghai Ruijin Hospital	(2008) EC REVIEW (34)
THE THIRD HOSPITAL OF HEBEI MEDICAL UNI	China	Ethics Committee of Shanghai Ruijin Hospital	(2008) EC REVIEW (34)
XINHUA HOSPITAL	China	Ethics Committee of Shanghai Ruijin Hospital	(2008) EC REVIEW (34)
ZHEJIANG HOSPITAL	China	Ethics Committee of Shanghai Ruijin Hospital	(2008) EC REVIEW (34)
ZHONGSHAN HOSPITAL FUDAN UNIVERSITY	China	Ethics Committee of Shanghai Ruijin Hospital	(2008) EC REVIEW (34)
BEIJING HAIDIAN HOSPITAL	China	Ethics Committee of Shanghai Ruijin Hospital	(2008) EC REVIEW (34)
BEIJING SHIJITAN HOSPITAL - SLEEP CENTER	China	Ethics Committee of Shanghai Ruijin Hospital	(2008) EC REVIEW (34)
BEIJING TONGREN HOSPITAL - DEP OF NEUROLOGY	China	Ethics Committee of Shanghai Ruijin Hospital	(2008) EC REVIEW (34)
NANJING JIANGNING HOSPITAL	China	Ethics Committee of Shanghai Ruijin Hospital	(2008) EC REVIEW (34)
THE SECOND AFFILIATED HOSP OF SOOCHOW UNI	China	Ethics Committee of Shanghai Ruijin Hospital	(2008) EC REVIEW (34)
THE FIRST HOSPITAL OF SHANXI MEDICAL UNI	China	Ethics Committee of The First Affiliated Hospital of Shanxi Medical University	SAVE
THE PEOPLES HOSP GUANGXI ZHUANG AUTONOM REG	China	Ethics Committee of Shanghai Ruijin Hospital	(2008) EC REVIEW (34)
THE FIRST PEOPLES HOSPITAL OF FOSHAN	China	Ethics Committee of Shanghai Ruijin Hospital	(2008) EC REVIEW (34)

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THE SECOND HOSPITAL OF SHANXI MEDICAL UNI	China	Ethics Committee of Shanghai Ruijin Hospital	(2008) EC REVIEW (34)
THE 1ST AFFILIATED HOSP OF BAOTOU MED COLL	China	Ethics Committee of Shanghai Ruijin Hospital	(2008) EC REVIEW (34)
THE SECOND AFF HOSP OF HEBEI MEDICAL UNI	China	Ethics Committee of Shanghai Ruijin Hospital	(2008) EC REVIEW (34)
HEJIAN MUNICIPAL PEOPLES HOSPITAL	China	Ethics Committee of Shanghai Ruijin Hospital	(2008) EC REVIEW (34)
SHANGHAI SHIDONG HOSPITAL	China	Ethics Committee of Shanghai Ruijin Hospital	(2008) EC REVIEW (34)
XUZHOU CENTRAL HOSPITAL	China	Ethics Committee of Shanghai Ruijin Hospital	(2008) EC REVIEW (34)
PEKING UNIVERSITY SHOUGANG HOSPITAL	China	Ethics Committee of Shanghai Ruijin Hospital	(2008) EC REVIEW (34)
JIANGSU PROVINCIAL HOPITAL OF STATE ORGAN	China	Ethics Committee of Shanghai Ruijin Hospital	(2008) EC REVIEW (34)
ZENGCHENG PEOPLES HOSPITAL	China	Ethics Committee of Shanghai Ruijin Hospital	(2008) EC REVIEW (34)
NO. 260 PLA HOSPITAL OF CHINA	China	Ethics Committee of Shanghai Ruijin Hospital	(2008) EC REVIEW (34)
THE FIRST PEOPLES HOSPITAL OF WUJIANG	China	Ethics Committee of Shanghai Ruijin Hospital	(2008) EC REVIEW (34)
BEIJING FRIENDSHIP HOSPITAL, CAPTIAL MED UNI	China	Ethics Committee of Beijing Friendship Hospital, Capital Medical University	(2011) EC REVIEW (053)
BEIJING TONGREN HOSPITAL, CARDIOLOGY DEPT.	China	Ethics Committee of Shanghai Ruijin Hospital	(2008) EC REVIEW (34)
ALL INDIA INSTITUTE OF MEDICAL SCIENCES	India	Institution Ethics Committee All India Institute of Medical Sciences	IEC/OP-01/05.12.2011
CHRISTIAN MEDICAL COLLEGE AND HOSPITAL	India	Institutional Ethics Committee Christian Medical College & Hospital, Ludhiana	None stated (SAVE)
KING EDVERD MEMORIAL HOSPITAL (KEM)	India	Ethics Committee for Research on Human Subjects (ECRHS), Seth G.S Medical College & K.E.M Hospital	EC/PHARMA-4/2010
B Y L NAIR HOSPITAL	India	Institutional Ethics Committee, B.Y.L NAIR CH. Hospital & T.N. MEDICAL COLLEGE	None stated (SAVE)
GLOBAL HOSPITAL	India	Institutional Ethics Committee, Global Hospitals	None stated (SAVE)
MEDICIT HOSPITAL	India	Mediciti Ethics Committee	None stated (SAVE)





VIJAYA HEALTH CENTER	India	The Ethics Committee Vinjaya Health Centre	None stated (SAVE)
CHEST CLINIC, SRI RAMA KRISHNA MEDICAL CENTRE	India	Institutional Ethics Committee, Ramakrishna Hospital	None stated (SAVE)
P S G HOSPITAL	India	PSG Institute of Medical Sciences & Research, Institutional Ethics Committee	None stated (SAVE)
HOSPITAL TXAGORRITXU	Spain	EUSKADI 'S CLINICAL RESEARCH OF ETHICS COMMITTEE	2011116
HOSPITAL PARC TAULI	Spain	Ethics Committee of Corporacio Sanitaria Parc Tauli	None stated (SAVE)
HOSPITAL DOCE DE OCTUBRE, MADRID	Spain	Ethics Committee 12 Octubre Hospital	11/187
HOSPITAL CENTRAL DE ASTURIAS	Spain	Comite Etico de Investigacion Clinica de Asturias	SAVE
HOSPITAL SANTA MARIA	Spain	Clinical Research Ethics Committee, Arnau de Vilanova University Hospital	None stated (SAVE)
HOSPITAL UNIVERSITARIO DE GUADALAJARA	Spain	Clinical Research Ethics Committee, Guadalajara University Hospital	None stated (SAVE)
MAYO CLINIC	USA	Mayo Clinic Institutional Review Boards	11-002685

**e-Table 2:** Medical history and medication at baseline

	CPAP Count	Column N %	Usual Care Count	Column N %	Total Count	Column N %
Hypertension	1043	78.5%	1032	78.2%	2075	78.3%
Diabetes mellitus	401	30.2%	387	29.3%	788	29.8%
Any heart disease	546	41.1%	523	39.6%	1069	40.4%
Myocardial infarction	426	32.1%	458	34.7%	884	33.4%
Angina	497	37.4%	478	36.2%	975	36.8%
Heart failure	19	1.4%	29	2.2%	48	1.8%
Valvular heart disease	20	1.5%	28	2.1%	48	1.8%
Percutaneous coronary revascularization (+-stent)	444	33.4%	455	34.5%	899	33.9%
Coronary artery bypass graft	158	11.9%	154	11.7%	312	11.8%
Stroke	582	43.8%	586	44.4%	1168	44.1%
Transient ischaemic attack	134	10.1%	128	9.7%	262	9.9%
Carotid endarterectomy or percutaneous stent	10	0.8%	12	0.9%	22	0.8%
Intracerebral stent	3	0.2%	2	0.2%	5	0.2%
Other form of cardiovascular disease	52	3.9%	64	4.8%	116	4.4%
Blood pressure lowering medication	1037	78.0%	1026	77.7%	2063	77.9%
Multiple BP modifying medications	668	50.3%	632	47.9%	1300	49.1%
Lipid lowering medication	752	56.6%	788	59.7%	1540	58.1%
Multiple lipid modifying drugs	77	5.8%	78	5.9%	155	5.9%
Oral anti-diabetic medication	288	21.7%	288	21.8%	576	21.7%
Insulin	79	5.9%	81	6.1%	160	6.0%
Anti-platelet/ anti-thrombotic agents	994	74.8%	994	75.3%	1988	75.0%
Organic nitrates	218	16.4%	204	15.5%	422	15.9%
Other cardiac medications	66	5.0%	54	4.1%	120	4.5%
Traditional Chinese medicines	144	10.8%	128	9.7%	272	10.3%
Alimentary tract and metabolism medications	21	1.6%	27	2.0%	48	1.8%

\*Note medical history information missing for 6 participants (3 in each treatment group)

**e-Table 3:** Characterization of sleep apnea metrics and patterns of nocturnal hypoxemia.

	CPAP Median (IQR)	Usual Care Median (IQR)	Total Median (IQR)
Apnoea-hypopnea index (AHI) [events/hour]	25 (16 – 38)	25 (16 – 40)	25 (16 – 39)
Epworth Sleepiness Score (ESS)	7 (5 – 10)	7 (5 – 10)	7 (5 – 10)
Average nightly adherence of sham CPAP [hours/night]	5.1 (4.1 - 6.2)	5.1 (4.1 - 6.2)	5.1 (4.1 – 6.2)
CPAP adherence over duration of trial [hours/night]	3.2 (1.2 - 5.0)	-	
Patterns of nocturnal hypoxemia (custom MATLAB® algorithm)			
Oxygen desaturation index (ODI) [events/hour]	21.8 (14.2 – 34.9)	22.1 (14.5 – 36.3)	22.0 (14.3 – 35.6)
T<90% (minutes)	25.8 (9.9 – 66.1)	24.8 (8.5 – 64.5)	25.4 (9.2 – 65.0)
Mean SpO <sub>2</sub> [%]	93.6 (92.1 – 94.7)	93.7 (92.2 – 94.8)	93.6 (92.2 – 94.7)
Baseline SpO <sub>2</sub> [%]	95.1 (93.8 – 96.2)	95.2 (93.8 – 96.3)	95.2 (93.8 – 96.2)
Desaturation SpO <sub>2</sub> [%]	1.1 (0.7 – 1.9)	1.1 (0.7 – 2.0)	1.1 (0.7 – 1.9)
Desaturation duration [s]	43.5 (37.0 – 49.5)	43.0 (37.0 – 49.0)	43.0 (37.0 - 49.0)
Desaturation/resaturation time ratio	1.8 (1.5 – 2.3)	1.8 (1.4 - 2.3)	1.8 (1.5 – 2.3)
Desaturation average SpO <sub>2</sub> reduction [%]	3.4 (2.9 – 4.1)	3.4 (2.9 – 4.1)	3.4 (2.9 – 4.1)
Desaturation nadir [%]	89.0 (88.0 – 91.0)	89.0 (88.0 – 91.0)	89.0 (88.0 – 91.0)

Oxygen desaturation index (ODI) as calculated by desaturation events identified by the custom algorithm, per hour of analysed recording time.

No significant differences between treatment groups.

**e-Table 4:** Multivariable Cox regression analysis for outcome components

	Cardiovascular Death			Myocardial Infarction			Stroke			Heart Failure			Angina			Transient Ischaemic Event		
	HR	95% CI	Sig	HR	95% CI	Sig	HR	95% CI	Sig	HR	95% CI	Sig	HR	95% CI	Sig	HR	95% CI	Sig
<b>Block 1</b>																		
Treatment allocation (CPAP vs Usual Care)			ns			ns			ns			ns			ns			ns
Smoking status (ref. never)			ns			ns			ns			ns			0.010			ns
Past			-			-			-			-	0.87	0.546, 1.382	0.539			-
Current			-			-			-			-	1.42	0.911, 2.206	0.122			-
Ethnicity, simplified (ref. Caucasian/European)			ns			0.041			0.051			ns			<0.0001			0.064
Asian			-	0.58	0.317, 1.073	0.083	1.83	0.998, 3.339	0.051			-	2.64	1.714, 4.053	<0.0001	0.32	0.120, 0.831	0.020
Other			-	1.45	0.767, 2.746	0.252	0.77	0.251, 2.373	0.651			-	0.98	0.500, 1.924	0.954	0.66	0.138, 3.155	0.603
Hypertension history			ns			ns			ns			ns			ns			ns
Diabetes			ns			ns	1.95	1.367, 2.770	<0.001			ns			ns			ns
Cardiovascular disease history (ref. cardiac only)			ns			0.015			<0.0001			ns			<0.0001			0.049
Cerebrovascular			-	0.69	0.386, 1.246	0.221	3.42	2.125, 5.501	<0.0001			-	0.29	0.192, 0.426	<0.0001	1.98	0.731, 5.384	0.179
Both			-	2.40	1.122, 5.121	0.024	7.02	3.691, 13.345	<0.0001			-	2.15	1.379, 3.342	0.001	5.32	1.386, 20.405	0.015
Medications (count)	1.28	1.094, 1.495	0.002	1.12	0.990, 1.257	0.072			ns	1.45	1.232, 1.705	<0.0001	1.12	1.033, 1.224	0.007	0.72	0.538, 0.960	0.025
Age (years)			ns			ns			ns	1.13	1.062, 1.193	<0.0001			ns			ns
Waist:hip ratio			ns	32.68	3.423, 311.965	0.002			ns			ns			ns			ns
Oxygen Desaturation Index (events/hour, custom)			ns			ns			ns			ns			ns			ns



<b>Block 2</b>																		
Pulse rate (mean)			ns			ns			ns	1.04	1.002, 1.075	0.037			ns		ns	
Pulse rate (standard deviation)	1.11	1.071, 1.156	<0.00 01			ns	1.04	1.006, 1.074	0.022			ns	0.91	0.826, 0.999	0.048		ns	
Desat/Resat time ratio			ns			ns			ns	0.32	0.151, 0.688	0.003			ns		ns	
Baseline SpO2 (%)	1.18	0.976, 1.437	0.086	0.90	0.795, 1.016	0.089			ns			ns	0.92	0.843, 1.004	0.063		ns	
Desaturation event average SpO2 reduction (%)	0.58	0.391, 0.868	0.008			ns			ns			ns			ns		ns	
Desaturation event duration (s)	1.04	1.006, 1.067	0.018			ns			ns	1.05	1.014, 1.079	0.005			ns	1.05	1.012, 1.087	0.010

ns indicates variables excluded from the backwards conditional stepwise multivariable Cox regression analysis as not significant. Variables were assessed for retention in each block as P(in) 0.05/P(out) 0.

**e-Table 5:** Heart failure outcome. The two block multivariable backwards stepwise multivariable Cox regression approach applied to the heart failure outcome only.

	<b>HR [95% CI]</b>	<b>HR, z-normalised value for scale variables [95% CI]</b>	<b>Sig.</b>
Medications sum	1.45 [1.23-1.71]	2.02 [1.48-2.75]	P<0.001
Age (years)	1.13 [1.06-1.19]	2.51 [1.60-3.94]	P<0.001
Pulse mean [bpm]	1.04 [1.00-1.08]	1.41 [1.02-1.96]	P=0.037
Desaturation/resaturation time ratio	0.32 [0.15-0.69]	0.48 [0.29-0.78]	P=0.003
Desaturation duration [s]	1.05 [1.01-1.08]	1.53 [1.14-2.05]	P=0.005

Regression formula for final model: 0.371\*medications sum + 0.118\*age at baseline (years) + 0.037\*mean pulse + (-1.131\*Desat/resat time ratio) + 0.045\*Desaturation duration

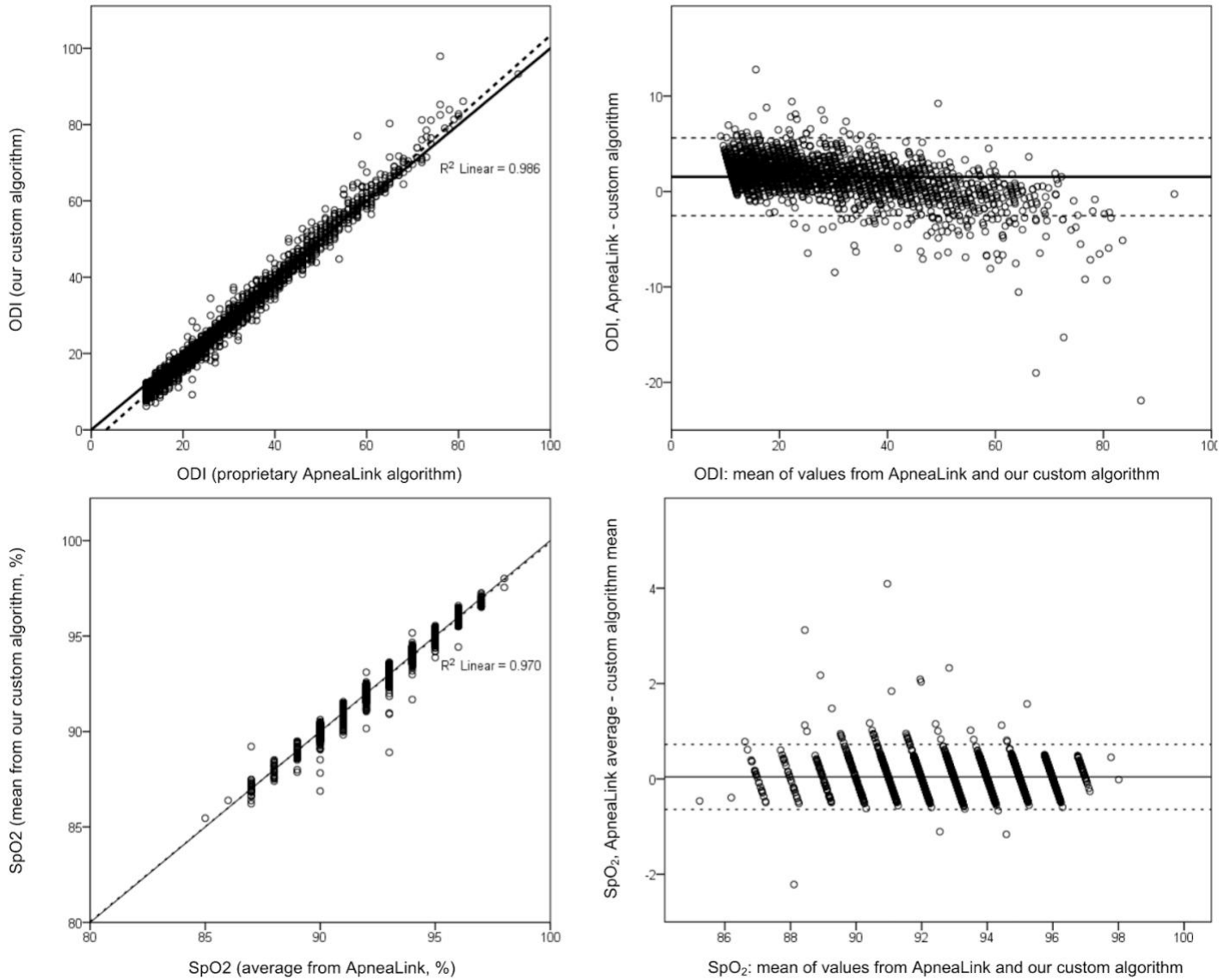
**e-Table 6:** Reanalysis of the heart failure outcome in a second two block backwards stepwise conditional analysis, in which the general cardiovascular disease history variable (coronary, cerebrovascular or both) in the first block was replaced with a categorical variable specific for history of heart failure.

	<b>HR [95% CI]</b>	<b>HR, z-normalised value for scale variables [95% CI]</b>	<b>Sig.</b>
Diabetes	2.30 [1.00-5.27]		P=0.049
Heart failure history	4.38 [1.67-11.48]		P=0.003
Medications sum	1.27 [1.04-1.55]	1.58 [1.08-2.31]	P=0.017
Age (years)	1.10 [1.04-1.16]	2.10 [1.35-3.27]	P=0.001
Desaturation/resaturation time ratio	0.39 [0.19-0.83]	0.55 [0.33-0.89]	P=0.015
Desaturation duration [s]	1.04 [1.01-1.08]	1.48 [1.09-2.00]	P=0.012

Regression formula for final model = 0.832\*1 (if diabetes, 0 if not) + 0.242\*medications sum + 0.095\*age at baseline + 1.477\*1 (if history of heart failure, 0 if not) + (-0.935\* desaturation/resaturation ratio) + 0.041\* desaturation duration.

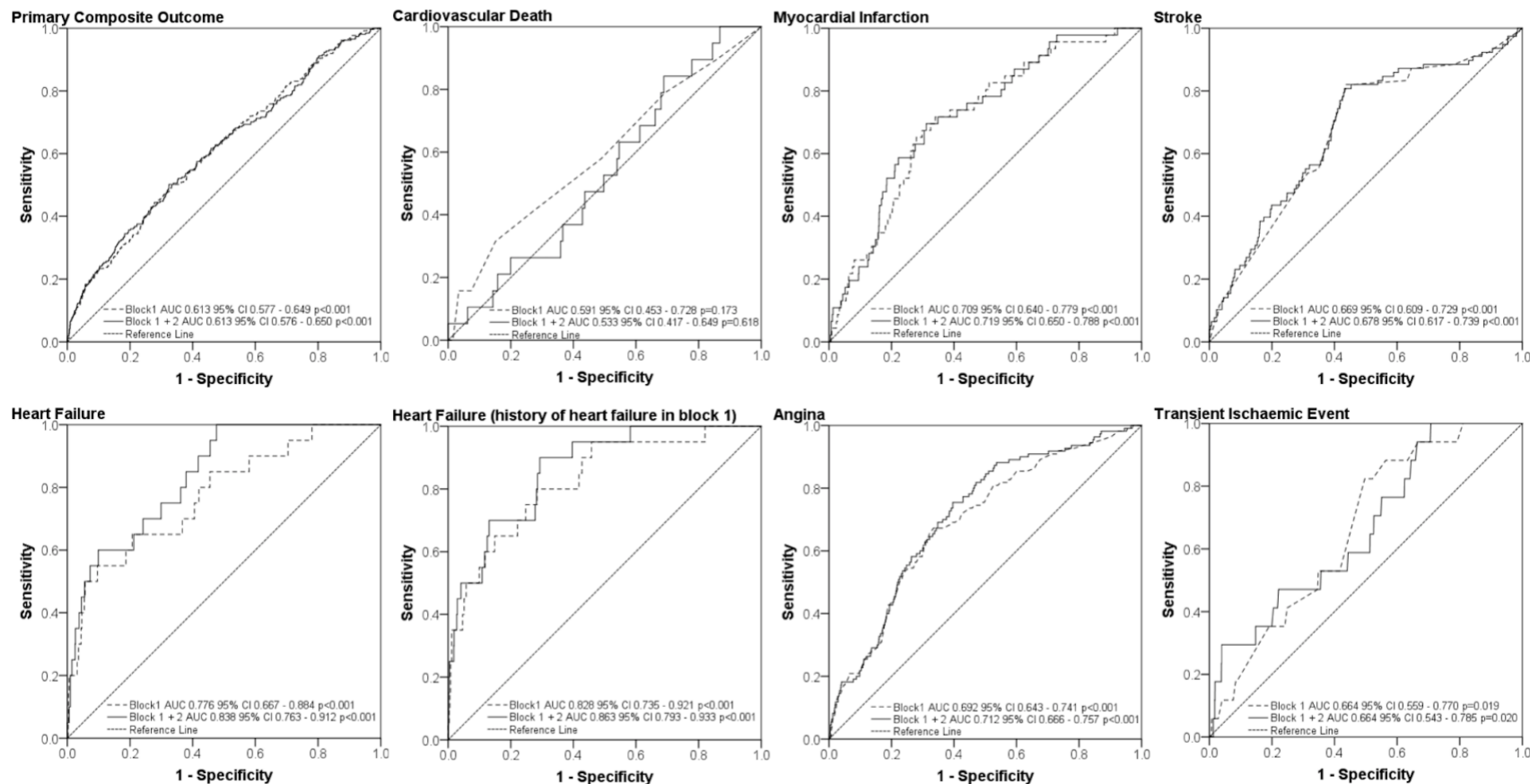


**e-Figure 1.**



Direct comparison and Bland-Altman plots comparing oxygen desaturation index (ODI, events/hour) and mean SpO<sub>2</sub> (%) calculated by the ApneaLink® software and by the custom MATLAB® algorithm.

**e-Figure 2.**



Receiver-Operator Characteristic Curves for two year outcomes in SAVE, with predictive equations from two block, backwards stepwise conditional multivariate Cox regression analyses. In each case, Block 1 was calculated using “standard” variables (treatment allocation, smoking status, ethnicity, hypertension history, diabetes status, cardiovascular disease history category, count of medications at baseline, age, waist:hip ratio, and oxygen desaturation index). Block 2 added novel metrics from pulse oximetry analyses (mean pulse rate and its standard deviation, baseline SpO<sub>2</sub>, and measures of identified desaturation events: desaturation/resaturation time ratio, average SpO<sub>2</sub> reduction and duration). Variables retained in the model were determined in each block by p(in) 0.05, p(out) 0.10.