11. Ito K, Hirooka Y, Matsukawa R, Nakano M, Sunagawa K. Decreased brain sigma-1 receptor contributes to the relationship between heart failure and depression. Cardiovasc Res. 93: 33-40, 2012.

12. Sugimachi M, Uemura K, Kawada T, Shishido T, Sunagawa K. Reduction of myocardial oxygen demand by controlling heart rate and hemodynamics simultaneously by novel circulatory model. Conf Proc IEEE Eng Med Biol Soc. 2011:4297-300, 2011.

13. Sakamoto T, Murayama Y, Tanaka A, Sakamoto K, Tobushi T, Saku K, Hosokawa K, Onitsuka K, Fujino T, Sunagawa K. Impact of baroreflex on venous return surface. Conf Proc IEEE Eng Med Biol Soc. 2011: 4295-4296, 2011.

14. Kishi T, Sunagawa K. Experimental 'jet lag' causes sympathoexcitation via oxidative stress through AT1 receptor in the brainstem. Conf Proc IEEE Eng Med Biol Soc. 2011: 1969-1972, 2011.

15. Hosokawa K, Funakoshi K, Tanaka A, Sakamoto T, Onitsuka K, Sakamoto K, Tobushi T, Fujino T, Saku K, Murayama Y, Ide T, Sunagawa K. Artificial baroreflex system restores volume tolerance in the absence of native baroreflex. Conf Proc IEEE Eng Med Biol Soc. 2011: 697-699, 2011.

16. Kawada T, Shimizu S, Sata Y, Kamiya A, Sunagawa K, Sugimachi M. Consideration on step duration to assess open-loop static characteristics of the carotid sinus baroreflex in rats. Conf Proc IEEE Eng Med Biol Soc. 2011: 689-692, 2011.

17. Masuda S, Nakano K, Funakoshi K, Zhao G, Meng W, Kimura S, Matoba T, Miyagawa M, Iwata E, Sunagawa K, Egashira K. Imatinib mesylate-incorporated nanoparticle-eluting stent attenuates in-stent neointimal formation in porcine coronary arteries. J Atheroscler Thromb. 18: 1043-1053, 2011.

18. Matsuura H, Ichiki T, Ikeda J, Takeda K, Miyazaki R, Hashimoto T, Narabayashi E, Kitamoto S, Tokunou T, Sunagawa K. Inhibition of prolyl hydroxylase domain-containing protein downregulates vascular angiotensin II type 1 receptor. Hypertension. 58: 386-393, 2011.

19. Ogawa K, Hirooka Y, Kishi T, Sunagawa K. Brain AT1 receptor activates the sympathetic nervous system through toll-like receptor 4 in mice with heart failure. J Cardiovasc Pharmacol. 58: 543-549, 2011.

20. Matsukawa R, Hirooka Y, Nishihara M, Ito K, Sunagawa K. Neuregulin-1/ErbB signaling in rostral ventrolateral medulla is involved in blood pressure regulation as an antihypertensive system. J Hypertens. 29: 1735-1742, 2011.

21. Kishi T, Hirooka Y, Ogawa K, Konno S, Sunagawa K. Calorie restriction inhibits sympathetic nerve activity via anti-oxidant effect in the rostral ventrolateral medulla of obesity-induced hypertensive rats. Clin Exp Hypertens. 33: 240-245, 2011.

22. Nakagaki T, Hirooka Y, Ito K, Kishi T, Hoka S, Sunagawa K. Role of angiotensin-(1-7) in rostral ventrolateral medulla in blood pressure regulation via sympathetic nerve activity in Wistar-Kyoto and spontaneous hypertensive rats. Clin Exp Hypertens. 33: 223-230, 2011.

23. Hashimoto T, Ichiki T, Ikeda J, Narabayashi E, Matsuura H, Miyazaki R, Inanaga K, Takeda K, Sunagawa K. Inhibition of MDM2 attenuates neointimal hyperplasia via suppression of vascular proliferation and inflammation. Cardiovasc Res. 91: 711-719, 2011.

24. Uemura K, Kawada T, Sunagawa K, Sugimachi M. Peak systolic mitral annulus velocity reflects the status of ventricular-arterial coupling-theoretical and experimental analyses. J Am Soc Echocardiogr. 24: 582-591, 2011.

25. Hirooka Y, Kishi T, Sakai K, Takeshita A, Sunagawa K. Imbalance of central nitric oxide and reactive oxygen species in the regulation of sympathetic activity and neural mechanisms of hypertension. Am J Physiol Regul Integr Comp Physiol. 300: R818-R826, 2011.

26. Chen L, Nakano K, Kimura S, Matoba T, Iwata E, Miyagawa M, Tsujimoto H, Nagaoka K, Kishimoto J, Sunagawa K, Egashira K. Nanoparticle-mediated delivery of pitavastatin into lungs ameliorates the development and induces regression of monocrotaline-induced pulmonary artery hypertension. Hypertension. 57: 343-350, 2011.

27. Fujino T, Nishizaka M, Yufu T, Sunagawa K. A case of multiple focal nodular hyperplasia in the liver which developed after heart transplantation. Intern Med. 50: 43-46, 2011

G-2.学会発表

1. Fujino T, Ide T, Yoshida M, Hata Y, Takehara T, Onitsuka K, Tanaka A, Takazaki S, Nishida M, Kang D, Sunagawa K: Recombinant TFAM attenuates pathological hypertrophy of cardiac myocytes via inhibiting NFAT signaling. Experimental Biology 2011
2. Funakoshi K, Hosokawa K, Tanaka A, Sakamoto T, Onitsuka K, Sakamoto K, Tobushi T, Fujino T, Saku K, Murayama Y, Ide T, Sunagawa K: Baroreflex failure may play a major role in the pathogenesis of heart failure with preserved ejection fraction.
3. Hosokawa K, Funakoshi K, Tanaka A, Sakamoto T, Onitsuka K, Sakamoto K, Tobushi T, Fujino T, Saku K, Murayama Y, Ide T, Sunagawa K: Artificial Baroreflex System Restores Volume Buffering Function in the Baroreflex Failure Irrespective of Left Ventricular Systolic Function.
4. Kishi T, Hirooka Y, Sunagawa K. Autoimplantation of astrocytes into cardiovascular center of brainstem causes sympathoinhibition and decreases the mortality rate in Hypertensive rats.
5. Matsukawa R, Hirooka Y, Ito K, Sunagawa K: Dysfunction of NRG-1/ErbB pathway modulating nitric oxide synthases in rostral ventrolateral medulla plays a pivotal role in central mechanisms of hypertension .
6. Nishihara M, Hirooka Y, Kishi T, Sunagawa K: Inhibition of Reactive oxygen species in rostral ventrolateral medulla augments sympathoexcitatory effects from the paraventricular nucleus of the hypothalamus in spontaneously hypertensive rats.
7. Ogawa K, Hirooka Y, Kishi T, Sunagawa K: Overexpression of MnSOD in the rostral ventrolateral medulla improves baroreflex function thereby inhibiting sympathetic activity of hypertensive rats.
8. Sakamoto T, Murayama Y, Sakamoto K, Tobushi T, Tanaka A, Saku K, Hosokawa K, Onitsuka K, Fujino T, Sunagawa K: Baroreflex changes only stressed volume not the slope of the venous return surface.
9. Shinohara K, Hirooka Y, Kishi T, Sunagawa K: Inhibition of nitric oxide-GABA pathway by reactive oxygen species in the rostral ventrolateral medulla causes sympathoexcitation in SHRSP.
10. Hosokawa K, Funakoshi K, Tanaka A, Sakamoto T, Onitsuka K, Sakamoto K, Tobushi T, Fujino T, Saku K, Murayama Y, Ide T, Sunagawa K: Artificial Baroreflex System Restores Volume Tolerance in the Absence of Native Baroreflex. 33rd Annual International Conference of the IEEE Engineering in Medicine and Biology Society
11. Kishi T, Sunagawa K: Experimental jet lag causes sympathoexcitation via oxidative stress through AT1 receptor in the brain. 33rd Annual International Conference of the IEEE Engineering in Medicine and Biology Society
12. Sakamoto T, Murayama Y, Tanaka A, Sakamoto K, Tobushi T, Saku K, Hosokawa K, Onitsuka K, Fujino T, Sunagawa K: Impact of Baroreflex on Venous Return Surface. 33rd Annual International Conference of the IEEE Engineering in Medicine and Biology Society
13. Kishi T, Hirooka Y, Sunagawa K: Autoimplantation of astrocytes into cardiovascular center of brainstem causes sympathoinhibition and decreases the mortality rate in Hypertensive rats. 7th Congress of the International Society for Autonomic Neuroscience: ISAN, 22nd Symposium of the American Autonomic Society
14. Sakamoto T, Murayama Y, Tanaka A, Tobushi T, Sakamoto K, Saku K, Hosokawa K, Onizuka K, Fujino T, Sunagawa K: Baroreflex changes only stressed volume not the slope of the venous return surface in anesthetized dogs. 7th Congress of the International Society for Autonomic Neuroscience: ISAN, 22nd Symposium of the American Autonomic Society
15. Sunagawa K. What the vagal nerve stimulation can do for the diseased heart? 7th Congress of the International Society for Autonomic Neuroscience: ISAN, 22nd Symposium of the American Autonomic Society
16. Sunagawa K. Vagus Nerve Stimulation in Heart Failure. ISAN/AAS-2011 Satellite Meeting
17. Sunagawa K. Bionic Baroreflex Control of Blood Pressure in Hypotensive & Hypertensive Disorders. ISAN/AAS-2011 Satellite Meeting
18. Nishihara M, Hirooka Y, Kishi T, Sunagawa K: Inhibition of oxidative stress in

paraventricular nucleus of the hypothalamus reduces heart rate, but not blood pressure in spontaneously hypertensive rats. High Blood Pressure Research 2011 Scientific Sessions

19. Fujino T, Ide T, Yoshida M, Onitsuka K, Tanaka A, Hata Y, Takehara T, Hosokawa K, Sakamoto T, Nishida M, Sunagawa K: Recombinant Mitochondrial Transcriptional Factor A Protein Attenuates Pathological Remodeling in Cardiac Myocytes. Scientific Sessions 2011, American Heart Association
20. Hirooka Y: Advances in neural control of circulation: from hypertension to heart failure. Scientific Sessions 2011, American Heart Association
21. Funakoshi K, Sunagawa K: Baroreflex Failure induces striking volume intolerance in a rat model with normal left ventricular function. Scientific Sessions 2011, American Heart Association
22. Hosokawa K, Funakoshi K, Sakamoto T, Onitsuka K, Sakamoto K, Tobushi T, Fujino T, Saku K, Murayama Y, Ide T, Sunagawa K: Artificial Baroreceptor Fully Antagonizes Baroreflex Failure Induced Volume Intolerance. Scientific Sessions 2011, American Heart Association
23. Ito K, Hirooka Y, Sunagawa K: The brain AT1R are responsible for sympathoexcitation associated with brain MR activation in mice with pressure overload after salt loading. Scientific Sessions 2011, American Heart Association
24. Kishi T, Hirooka Y, Sunagawa K: Autoimplantation of Astrocytes into the Cardiovascular Center of Brainstem Causes Sympathoinhibition and Decreases the Mortality Rate in Myocardial Infarction-Induced Heart Failure. Scientific Sessions 2011, American Heart Association
25. Kishi T, Hirooka Y, Sunagawa K: Combination Therapy of Amlodipine with Atorvastatin Suppresses Sympathetic Nerve Activity and Improves Cognitive Function Independent of Depressor Effects.Scientific Sessions 2011, American Heart Association
26. Kishi T, Hirooka Y, Sunagawa K: Oral Administration of Telmisartan Causes Sympathoinhibition through the Blockade of AT1 Receptor in the Cardiovascular Center of Brainstem and the Activation of the Systemic PPAR-gamma in Metabolic Syndrome. Scientific Sessions 2011, American Heart Association
27. Matsukawa R, Hirooka Y, Ito K, Sunagawa K: Attenuating ErbB2 signaling in the rostral ventrolateral medulla reduces nitric oxide synthesis and induces hypertension. Scientific Sessions 2011, American Heart Association
28. Matsukawa R, Hirooka Y, Ito K, Sunagawa K: Central NRG-1/ErbB signaling has a pivotal role in sympathoexcitation in heart failure. Scientific Sessions 2011, American Heart Association
29. Nakagaki T, Hirooka Y, Ito K, Matsukawa R, Nishihara M, Hoka S, Sunagawa K: Activation of mineralocorticoid receptors in the rostral ventrolateral medulla enhances sympathetic activity in stroke-prone spontaneously hypertensive rats. Scientific Sessions 2011, American Heart Association
30. Ogawa K, Hirooka Y, Kishi T, Suanagwa K: Inhibition of the Toll-like receptor 4 in the brainstem causes the sympathoinhibition and improves the left ventricular systolic dysfunction in heart failure. Scientific Sessions 2011, American Heart Association
31. Ogawa K, Hirooka Y, Kishi T, Sunagawa K: Inhibition of ROS in the rostral ventrolateral medulla improves baroreflex function in stroke-prone spontaneously hypertensive rats. Scientific Sessions 2011, American Heart Association
32. Shinohara K, Hirooka Y, Kishi T, Sunagawa K: Inhibition of NO-mediated GABA release by reactive oxygen species in the rostral ventrolateral medulla results in sympathoexcitation in hypertensive rats. Scientific Sessions 2011, American Heart Association
33. 坂本隆史、村山佳範、坂本和生、田中敦士、朔啓太、細川和也、鬼塚健、藤野剛雄、砂川賢二：動脈反射が静脈環流平面に与える影響：モデルに基づく解析と実験的検証 第 50 回日本生体医工学会大会
34. 船越公太、細川和也、田中敦士、坂本隆史、鬼塚健、坂本和生、戸伏倫之、藤野剛雄、朔啓太、村山佳範、井手友美、砂川賢二：圧反射異常は駆出率の保たれた心不全において重要な役割を果たす． 第 50 回日本生体医工学会大会
35. 細川和也、船越公太、田中敦士、坂本隆史、鬼塚健、坂本和生、戸伏倫之、藤野剛雄、朔啓太、村山佳範、井手友美、砂川賢二：

人工圧受容器システムは循環容量制御を再生する　第 50 回日本生体医工学会大会

36. 小河清寛、廣岡良隆、岸拓弥、砂川賢二：心不全マウスにおける交感神経活動亢進機序に脳内 AT_1 受容体を介した Toll-like receptor 4 の活性化が関与している　第 32 回日本循環制御医学会総会

37. 坂本隆史、村山佳範、坂本和生、戸伏倫之、田中敦士、朔啓太、細川和也、鬼塚健、藤野剛雄、砂川賢二：動脈圧反射が静脈還流平面に与える影響：モデルに基づく解析と実験的検証．　第 32 回日本循環制御医学会総会

38. 中垣俊明、廣岡良隆、西原正章、伊藤浩司、外須美夫、砂川賢二：脳卒中易発症生自然発症高血圧ラットにおける心臓血管中枢（RVLM）のミネラロコルチコイド受容体の活性化が交感神経系を介した血圧上昇に関与している．　第 32 回日本循環制御医学会総会

39. 船越公太、細川和也、田中敦士、坂本隆史、鬼塚健、坂本和生、戸伏倫之、藤野剛雄、朔啓太、村山佳範、井手友美、砂川賢二：圧反射異常は駆出率の保たれた心不全において重要な役割を果たす．　第 32 回日本循環制御医学会総会

40. 細川和也、船越公太、坂本隆史、鬼塚健、坂本和生、戸伏倫之、藤野剛雄、朔啓太、井手友美、砂川賢二：バイオニック圧受容器システムは循環容量制御を再生する　第 32 回日本循環制御医学会総会

41. 松川龍一、廣岡良隆、伊藤浩司、砂川賢二：中枢性血圧調節における RVLM 内 Neuregulin-1/ErbB signaling の役割 -作用機序および病態モデルにおける検討　第 32 回日本循環制御医学会総会

42. Fujino T, Ide T ,Yoshida M, Hata Y, Takehara T, Onitsuka K, Tanaka A, Sunagawa K.　Recombinant TFAM Attenuates Pathological Hypertrophy of Cardiac Myocytes via Inhibiting NFAT Signaling.　第 75 回日本循環器学会学術集会

43. Kishi T, Hirooka Y, Sunagawa K: Autoimplantation of astrocytes into cardiovascular center of brainstem causes prolonged sympathoinhibition and decreases the mortality rate in Hypertensive rats.　第 75 回日本循環器学会学術集会

44. Kishi T, Hirooka Y, Sunagawa K: Autoimplantation of astrocytes into cardiovascular center of brainstem improves the impaired baroreflex sensitivity and circadian rhythm of blood pressure.　第 75 回日本循環器学会学術集会

45. Kishi T, Hirooka Y, Sunagawa K: Telmisartan inhibits sympathetic activity through AT1R blockade in cardiovascular center of brainstem and activation of systemic PPAR-gamma in metabolic syndrome.　第 75 回日本循環器学会学術集会

46. Matsukawa R, Hirooka Y, Ito K, Sunagawa K: Inhibition of ErbB2 in the rostral ventorolateral medulla modulating nitric oxide - gamma-aminobutyric acid axis plays a pivotal role in neural hypertension.　第 75 回日本循環器学会学術集会

47. Nishihara M, Hirooka Y, Matsukawa R, Kishi T, Sunagawa K: Reactive oxygen species in rostral ventrolateral medulla attenuate γ–aminobutyric acid-ergic sympathoinhibition and augment symapthoexcitatory inputs from hypothalamus in hypertension.　第 75 回日本循環器学会学術集会

48. Ogawa K, Hirooka Y, Kishi T, Sunagawa K: Impaired baroreflex sensitivity due to increase oxidative stress in the rostral ventrolateral medulla contributes to sympathetic drive.　第 75 回日本循環器学会学術集会

49. Ogawa K, Hirooka Y, Kishi T, Sunagawa K: Toll-like receptor 4 activated by angiotensin II type 1 receptor in the brainstem contributes to sympathoexcitation in heart failure.　第 75 回日本循環器学会学術集会

50. Shinohara K, Hirooka Y, Kishi T, Sunagawa K: Inhibition of nitric oxide-GABA pathway due to reactive oxygen species in rostral ventrolateral medulla causes sympathoexcitation in SHRSP.　第 75 回日本循環器学会学術集会

51. Fujino T, Ide T, Yoshida M, Onitsuka K, Tanaka A, Hosokawa K, Sakamoto T, Sakamoto K, Tobushi T, Sunagawa K. Recombinant TFAM protein attenuates pathological hypertrophy of cardiac myocytes via inhibiting NFAT signaling.　第 15 回日本心不全学会学術集会

52. Matsukawa R, Hirooka Y, Ito K, Sunagawa K: The role of central NRG-1/ErbB signaling in heart failure of pressure overload model. 第 15 回日本心不全学会学術集会

53. Fujino T, Ide T, Yoshida M, Tanaka A, Onitsuka K, Ikeda M, Hata Y, Takehara T, Hosokawa K, Sakamoto T, Sakamoto K, Tobushi T, Nishida M, Kang D, Sunagawa K: Recombinant TFAM Inhibits NFAT Signaling and Attenuates Pathological Hypertrophy of Cardiac Myocytes. 第 28 回国際心臓研究学会

54. Hosokawa K, Funakoshi K, Takafumi Sakamoto, Ken Onitsuka, Kazuo Sakamoto, Tomoyuki Tobushi, Takeo Fujino, Keita Saku, Masataka Ikeda, Takamori Kakino, Yoshinori Murayama, Tomomi Ide, Sunagawa K: Artificial Baroreceptor System Restores Physiological Volume Buffering Function in Pulmonary Edema Induced by Baroreflex Failure. 第 28 回国際心臓研究学会

55. Ogawa K, Hirooka Y, Kishi T, Sunagawa K: Brain inflammation mediated by AT1 receptor-activated Toll-like receptor causes sympathoexcitation in myocardial infarction-induced heart failure. 第 28 回国際心臓研究学会

56. Sakamoto T, Murayama Y, Tobushi T, SakamotoK, Tanaka A, Saku K, Hosokawa K, Onizuka K, Fujino T, Funakoshi K, Sunagawa K: Changes in vascular properties, not ventricular properties, predominantly contribute to baroreflex regulation of arterial pressure. 第 28 回国際心臓研究学会

57. Honda N, Hirooka Y, Matsukawa R, Ito K, Sunagawa K: Central sympathoinhibition improves the prognosis of heart failure in salt loading induced-hypertensive rat. 第 76 回日本循環器学会総会・学術集会

58. Ito K, Hirooka Y, Sunagawa K: Activation of brain mineralocorticoid receptors through both aldosterone synthesis and 11□-HSD-2 deficiency contributes to salt-induced sympathoexcitation in mice with pressure-overload. 第 76 回日本循環器学会総会・学術集会

59. Ito K, Hirooka Y, Sunagawa K: ENaCs contributes to salt-induced sympathoexcitation via minelarocorticoid receptor activation and insufficient activation of CYP-EET pathway in mice with pressure-overload. 第 76 回日本循環器学会総会・学術集会

60. Kishi T, Hirooka Y, Sunagawa K: Autoimplantation of Astrocyte into Cardiovascular Center of Brainstem Markedly Improves Survival Rate of Post-myocardial Infarction Heart Failure Rats through Sympathoinhibition.第 76 回日本循環器学会総会・学術集会

61. Kishi T, Hirooka Y, Sunagawa K: Combination of Amlodipine and Atorvastatin Causes Sympathoinhibition and Improves Cognitive Function Independent of Blood Pressure-lowering Effects in Hypertensive Rats. 第 76 回日本循環器学会総会・学術集会

62. Matsukawa R, Hirooka Y, Ito K and Sunagawa K: Activation of central NRG-1/ErbB signaling improves cardiac function in heart failure with pressure overload through sympathoinhibiton. 第 76 回日本循環器学会総会・学術集会

63. Nakagaki T, Hirooka Y, Ito K, Matsukawa R, Nishihara M, Hoka S, Sunagawa K: Activation of mineralocorticoid receptors in the rostral ventrolateral medulla enhances sympathetic nerve activity in stroke-prone spontaneously hypertensive rats. 第 76 回日本循環器学会総会・学術集会

64. Nishihara M, Hirooka Y, Sunagawa K: Chronic reduction of oxidative stress in paraventricular nucleus decreases heart rate by modulating autonomic nervous system in spontaneously hypertensive rats. 第 76 回日本循環器学会総会・学術集会

65. Onitsuka K, Ide T, Arai S, Murayama Y, Kato Y, Takehara T, Hosokawa K, Sakamoto T, Sakamoto K, Tobushi T, Fujino T, Saku K, Ikeda M, Kakino T, Sunagawa K: Isolated Pure Systolic Stress Upregulates Hypertrophy-related Genes, Whereas Isolated Diastolic Strain Upregulates Fibrosis-related Genes. 第 76 回日本循環器学会総会・学術集会

66. Sakamoto T, Murayama Y, Sakamoto K, Tobushi T, Saku K, Hosokawa K, Onitsuka K, Fujino T, Ide T, Sunagawa K: Baroreflex Modulates Only Stressed Volume Not the Slope of the Venous Return Surface. 第 76 回日本循環器学会総会・学術集会

67. Shinohara K, Hirooka Y, Kishi T, Sunagawa K: Blockade of Angiotensin II Type 1 Receptor in the Brain Decreases Angiotensin II-induced Elevated Left Ventricular End-diastolic Pressure via

Sympathoinhibition. 第 76 回日本循環器学会総会・学術集会

68. Shinohara K, Hirooka Y, Kishi T, Sunagawa K: Combination Therapy of Olmesartan and Azelnidipine Inhibits Sympathetic Activity with the Antioxidant Action on the Brain in Hypertensive Rats. 第 76 回日本循環器学会総会・学術集会

69. Tobushi T, Hosokawa K, Murayama Y, Onitsuka K, Sakamoto T, Sakamoto K, Fujino T, Saku K, Ikeda M, Kakino T, Sunagawa K :Renal Afferent Nerve Stimulation Induces Baroreflex Resetting through the Activation of Sympathorenal Axis without Compromising Arterial Pressure Buffering Function 第76回日本循環器学会総会・学術集会

G-3.新聞報道

なし

H.知的所有権の取得状況

1. 砂川賢二
   動脈厚反射機能障害に関連した疾患を治療するためのバイオニック動脈圧反射システム
   出願日：2011 年 9 月 21 日
   出願番号：PCT/JP2011/071470

2. 砂川賢二、杉町勝、佐藤隆幸
   CARDIAC PACING SYSTEM, BLOOD PRESSURE REGULATING SYSTEM, AND CARDIAC DISEASE TREATMENT SYSTEM BY SUBSTITUTING NATIVE BIOLOGICAL REGULATORY FUNCTION
   特許取得：2011 年 6 月 14 日
   特許番号：US 7,962,216 B2

厚生労働省科学研究補助金
（医療機器開発推進研究事業）

平成２３年度分担研究報告書

慢性心不全の予後を改善するための非侵襲で安全・安心な無痛性 ICD の実用化臨床試験
デバイスサイクルの計画と調整 臨床試験の実行に関する研究

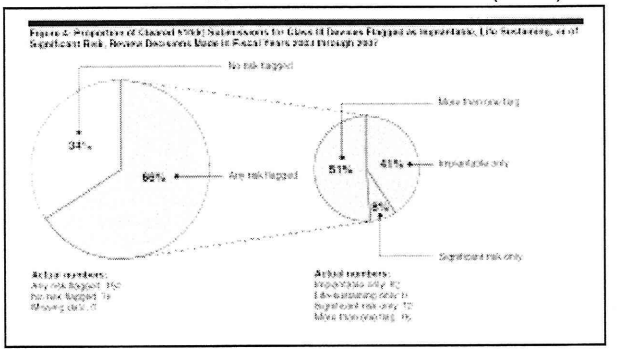
分担研究者　戸高　浩司　九州大学病院　循環器内科　特任准教授

研究要旨：
米国で ICD を始めとする高リスク医療機器の規制方針が近年変わりつつあり、本邦での ICD 開発にも影響を与えると考えられたため調査研究を行った。薬剤溶出性ステントの遅発性血栓症、ICD リコールなどをきっかけに米国では医療機器の規制が強化される方向にある。具合的には 510(k)と呼ばれる中等度リスク向けの認証制度を用いて高リスク機器が評価、市販が許可される場合があり、米国政府監査院より FDA が改善を指示された。いずれは class III の高リスク機器は全て PMA という臨床試験を課す本来の制度で評価、承認、市販許可されるという形に一本化されるものと考えられる。
規制を単に強化すると開発者側の負担が重くなるため軽減させる方法が幾つか提案されている。①市販前臨床試験を adaptive design や win ratio などを用いて規模を小さくする試み、②市販後に評価の重点（主に安全性）を移し、万が一生じた不具合に迅速に対応できるようする DELTA などの解析方法の試みなどがある。
後者に関しては市販後のレジストリーの充実が欠かせず、本邦でも医療機器や機器を使用した治療例を登録する制度整備が早急に望まれる。

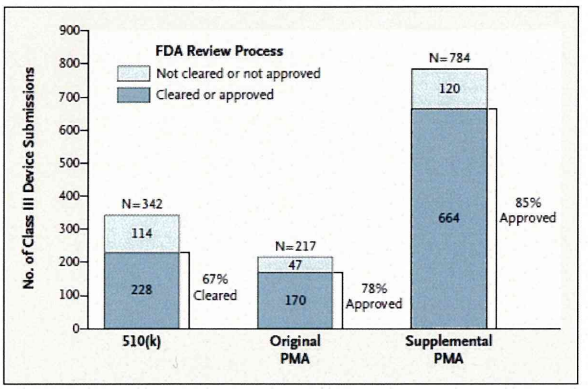
A.研究目的
高リスクデバイスに係る規制の日米比較、最近の動向、今後の方向性について明らかにする。

B.研究方法
１．最近の米国医療機器規制動向
Advamed、HBD thinktank west 2011 会議、AHA に参加発表し最新動向を調査した。
２．今後の医療機器規制の方向性
上記を受けて文献的考察を加え、本邦における手法について提言する。

C.研究結果
１．最近の米国医療機器規制動向
米国での class III (本邦のクラス III-IV に相当)機器は原則として PMA（市販前承認申請）が必要とされ、臨床試験が必須となるが、複数の別経路も存在する。preamendment class III device 注* を先行機器とみなす新機器は class III であっても本来 class II 用の制度である 510(k)による SE（本質的同等性）証明で clearance（認証）、市販が認められている。一方、革新的医療機器では類似した先行機器が無い場合が多く自動的に class III となり PMA が要求されていた。1997 年 FDA 近代化法により 510(k)による申請であっても de Novo process（classification）という class I-II に再分類する筋道が用意された。主にこれら２つの例外により本来 class III の機器が 510(k)という原則臨床試験を課さない、申請者に負担の少ない認証方法で市場に出ている。前者の preamendment class III device は歴史的に決まっており、IABP、VAD（心室補助装置）、ペースメーカ電極など植込み型、生命維持に直結するものも多く含まれている。
（注＊：1976 年に Medical Device Amendments が立法化される以前に市販されていた機器）
2009 年に United States Government Accountability Office, GAO（政府監査院）が 2003-2007 年度に 510(k)申請された 342 の class III device を調査したところ 228 (67%)が



そのまま認証、販売許可されている。同 office はこれを不適切として直ちに class II 以下に再分類するか、class III に残る機器（上図、228 のうち 66%は何らかの高リスク因子あり、class III を示唆）に関しては PMA を必須とするよう保健福祉長官から FDA に勧告することを求めていた。



Decisions about Class III Device Submissions by the FDA in Fiscal Years 2003–2007, According to FDA Review Process.

2010 年には NEJM にこの報告を引用した perspective（N Engl J Med 362;13 2010）も出された。これを受けて FDA は第三者として IOM（Institute of Medicine アメリカ医学研究所）に 510(k)制度の評価を依頼し、2011 年に報告が出された。その中で 8 つの勧告がなされており、class II に関しては PMS 市販後調査、登録による安全対策などを中心とした抜本的な改革、class III については 510(k)で認証されないよう求めている。

ICD については class III で PMA が求められるが 2005 年にリコールされた ICD の承認が簡易型の supplemental PMA でなされたこともあり、先の NEJM perspective の中で米国の高リスク医療機器規制に根本的な欠陥があるのではないかとの疑念が持たれ、GAO、IOM の報告とあいまって米国は以前より医療機器規制が厳格な方向へ進みつつある。

米国医療機器業界の集まりである AdvaMed 2011 では特に 510(k)制度改革に関する関心が高く複数のセッションが組まれていた。510(k)の審査が現に遅くなりつつある、ベンチャー企業が欧州へ逃げ出しつつあるなど、危機感をもった発表が大多数を占めた。

米国医療機器規制変化に関する AdvaMed sessions

- US VS. EU REGULATORY SYSTEMS: IMPACT OF THE DEVICE LAG
- IMPACT OF THE 510(K) REVIEW PROCESS CHANGES
- CRAGTING A USEFUL UDI SYSTEM
- CHALLENGES IN THE PRE-IDE/IDE PROCESS AND POTENTIAL SOLUTIONS
- POSTMARKET SURVEILLANCE: IMPORVING MAUDE

2．今後の医療機器規制の方向性

510(k)制度の改革に関しては既に始まったものとして米国では受け入れざるを得ないものとなっている。

PMA（や 510(k)の一部）で臨床試験を求められた場合に負担軽減をどのようにすれば良いか、臨床試験をどのように実行すべきかという大きな命題として近年議論されている。

AHA 年会においても以下のような複数のセッションが組まれていた。

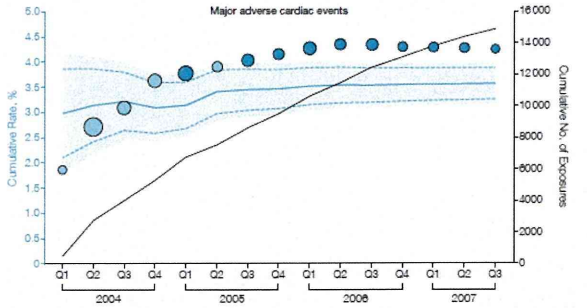
- Developing Cardiovascular Therapeutics in the 21st Century
- Efficacy and Effectiveness of Cardiovascular Therepeutics: Tools for Evaluation
- PMS of Drugs and Devices

医療機器の治験では無作為化二重盲検試験は多くの場合困難である。又、被検者の偏り（女性子供高齢者が少ない）、厳格な組入れ・除外基準などから来る外的妥当性の乏しさ、コスト・規模から確実に証明可能な小さな変化を見に行く試験（me-too 製品）が多くなる傾向など無作為化試験の限界、弊害も指摘されてきている。

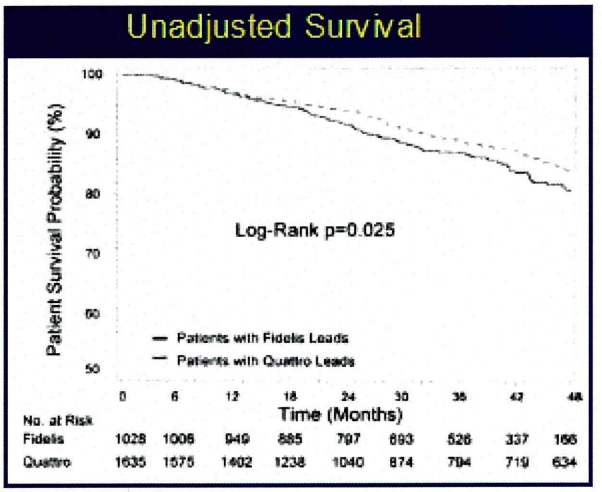
無作為化試験の難易度を下げコスト削減につながる方法として FDA は Duke 大学と共同で Clinical Trial Transformation Initiative を立ち上げ、例えば以下のような方法を提案している。
Adaptive trial design：中間解析を活用し無駄な群を中断するなど
Bayesian approach
Win ratio：複合 EP を用いると最初のイベントのみをカウントすることになる。それに対して死亡など重要なものから階層的に検証する方法。一般に検出パワーがあがる。

FDA's Regulatory Science White Paper の中で clinical trial simulation modeling といったコンピュータシミュレーションを用いて、最適な臨床試験法設計を事前に知ったり、将来的には臨床試験そのものを不要とするような方法も検討されつつある。

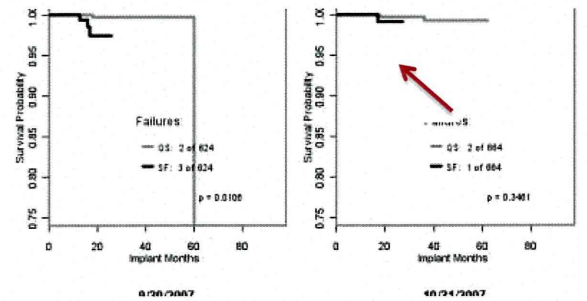
現在実行可能な対策として市販前に全ての証明を求めるのではなく、市販後のレジストリーを活用する方法が研究者、FDA 双方から提案されている。All-comer タイプの登録であれば外的妥当性の問題は無く、又例数が多いため小さな差も検出しやすい。例としてマサチューセッツ州の血管形成術登録による解析が上げられている（JAMA. 2010;304(18):2019-2027）。



DELTA, data extraction longitudinal trend analysis と名付けられたネットワークベースの解析方法を用いて TaxusExpress2 ステントで発生した MACE（上図丸印）が上市後 15 ヶ月足らずで他の DES（水色の帯：95%信頼領域）より多くなり有効性・安全性に懸念ありと判断できた。冠動脈ステントについては MACE が有効性指標でもある。



レジストリーを有効活用すれば市販後のリコールなどの対処が迅速にできたであろうケースも報告されている。ICD のリードが植込み後数年してから断線する不具合（Sprint Fidelis）でリコールがされたのは発売後 3 年ほど経った後で、通常の市販後調査により上図のような従来品との生存率の差が統計的に明らかになってからである。このリードは従来品より細かったために



発売後盛んに使われリコールされるまでの間に 1000 例ほどに植え込まれた。後ろ向きに一部の施設登録を用いて従来型の同社製品と不具合率を前述の DELTA で比較すると 13 ヵ月後には既に警告を出すレベルに達していることが分かった（上図）。

米国においては上記のマサチューセッツ州 PCI レジストリーや全国レベルの VAD レジストリーである INTERMACS などが元々多く存在し、これらの手法を用い得るインフラが整っている。

D.考察

比較的医療機器の規制が緩やかであると言われた米国でさえ安全性に関する要求が高まりつつある。近年、薬剤溶出性ステントの遅発性血栓症、ICD リコール、また薬ではあるが rofecoxib による心筋梗塞発生など頻度が高くないものの、時間が経ってから発生する重篤な副作用が市販後に相次いで明らかとなり社会的な問題となったことが背景にある。米国が取った対策は上述のように一部市販前の証明を厳しくするものであったが、むしろ市販後に証明の重点を移している。例えば同時期に出された薬剤溶出性ステントの評価ガイドラインでは初めて FDA が数年間の市販後調査を義務づけ、遅発性血栓症の報告をさせるという現実的なものであった。

ただ、これらの現実的対策であっても米国業界での評判は芳しくない。AdvaMed においては” US vs EU regulatory systems: impact of the Device Lag”という欧州に比しての米国のデバイスラグに関するセッションが組まれ現状でも 98%は欧州が先に承認されている、CE マークシステムのようなものを導入しないと、益々ラグは広がるので規制を強化すべきではない、方向性を誤ると「日本のように遅れすぎて機器によっては全く導入されないような事態になってしまう」といった意見まであった。全体としては FDA も含めて医療機器産業を国策として支持する姿勢が鮮明であった。

本邦においては米国とのデバイスラグが問題となっているが、承認制度そのものの違いも原因の一つである。例えば米国では VAD が preamendment class III device であり 510(k)により承認されうる。実際に Impella という小型の経皮的に挿入可能な革新性の高い VAD も 510(k)で承認されている。そのため僅か 16 例の単群試験により認証されている。本邦では class IV となり PMDA による通常の審査とならざるを得ずハードルはかなり高くなる。

上述のようなレジストリーを活用する方法に関しても、そもそも本邦において利用可能なレジストリーはどの領域でも少なく、人工心臓（VAD）の J-MACS、日本成人心臓血管外科手術データベース（JACVSD）などがあるくらいである。最近検討され始めたがん治療のレジストリーなど徐々に整備されつつはあるがかなり遅れており、historical control の必要が生じた場合等に常に問題になって来ている。

E.結論

ICD を始めとする植込み型医療機器の規制は市販後の安全性監視、迅速な対応に重点が移りつつあり、本邦においてもまずはレジストリーを全ての疾患領域に早急に整備する必要があると考えられる。

F.健康危険情報

該当なし。

G.研究発表

1. 学会発表

1. Takai E, Chen E, Laschinger J, Suzuki Y, Ikeda K, Sase K, Todaka K Japan-USA Harmonization by Doing New challenge for single protocol global clinical trial - proposed direction for WG 1 AdvaMed 2011, the MedTech conference (9/26-28, Washington DC, USA)

H.知的所有権の取得状況

特になし。

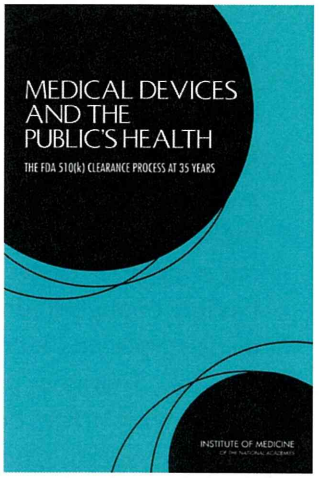
別添１．　IOM report on 510k

INSTITUTE OF MEDICINE
OF THE NATIONAL ACADEMIES
Advising the nation • Improving health

For more information visit www.iom.edu/510kprocess

Medical Devices and the Public's Health

The FDA 510(k) Clearance Process at 35 Years



Medical devices play a critical role in the health care of Americans. They can range from simple tools, such as tongue depressors and bandages, to complex or life-saving equipment, such as pacemakers, magnetic resonance imaging machines, and heart–lung machines. Devices are used in healthcare facilities—such as hospitals, physicians' offices, and nursing homes—and at home.

The Federal Food, Drug, and Cosmetic Act (FFDCA) requires a "reasonable assurance of safety and effectiveness" before a device can be marketed. The U.S. Food and Drug Administration (FDA) is responsible for enforcing this requirement. Devices that are deemed to have a moderate risk to patients generally cannot go on the market until they are cleared through the 510(k) process, named for Section 510(k) of the FFDCA. Devices that are subject to the 510(k) process include such devices as blood pressure cuffs as well as some types of contact lenses and pacemakers. The FDA received about 4,000 510(k) submissions in 2009.

Devices that are deemed to have a moderate risk to patients generally cannot go on the market until they are cleared through the 510(k) process, named for Section 510(k) of the FFDCA.

Some policymakers and patients have expressed concern about the ability of the 510(k) process to ensure that medical devices on the market are safe and effective. Other policymakers and patients, as well as the medical-device industry, have asserted that the process has become too burdensome and time-consuming and that it is delaying important new medical devices from entering the market.

The FDA turned to the Institute of Medicine (IOM), which appointed a committee to review the 510(k) process and answer two questions:

- Does the current 510(k) process protect patients optimally and promote innovation in support of public health?

- If not, what legislative, regulatory, or administrative changes are recommended to achieve the goals of the 510(k) process optimally?

The Legislative Framework of the 510(k) Process

Regulation of medical devices began in 1938 and reflected the relatively simple devices on the market at that time. By the 1970s, the original regulatory system no longer was adequate or flexible enough to deal with the growing array of device types and increasing sophistication of new devices. Sporadic public-health disasters associated with a few devices generated substantial public concern. Consequently, Congress passed the *Medical Device Amendments of 1976*, which established the framework for the current regulatory system, including the 510(k) process. Then, in 1990 and 1997, Congress passed sets of substantial changes to the 1976 statute. These three enactments serve as the basis of the legislative framework for the 510(k) process.

The law states that a moderate-risk device that is *substantially equivalent*, or similar, to any previously 510(k)-cleared device or any device that was on the market when the Medical Device Amendments were enacted—referred to as a *predicate device*—can be cleared for marketing with some exceptions. When the FDA assesses the substantial equivalence of a device, it generally does not require evidence of safety or effectiveness; and when a device is found to be substantially equivalent to a predicate device, the new device is assumed to be as safe and effective as the predicate because of its similarity. Devices that were on the market before the Medical Device Amendments were never systematically assessed for safety and effectiveness—but they are being used as predicate devices. This leads the committee to find that 510(k) clearance is not a determination that the cleared device is safe or effective. The committee concludes that the 510(k) process lacks the legal basis to be a reliable premarket screen of the safety and effectiveness of moderate-risk devices and, furthermore, that it cannot be transformed into one.

The committee is not suggesting that all, many, or even any medical devices cleared through the 510(k) process and currently on the market are unsafe or ineffective. The continual use of many of these devices in clinical practice provides reason for a level of confidence in their safety and effectiveness.

Innovation and the 510(k) Process

The committee defines innovation as something that improves the quality of, efficiency of, or access to health care. The 510(k) process does not require a moderate-risk device to be innovative, nor does it reward innovation. However, the 510(k) process can facilitate innovation by making new devices available to consumers in a timely manner.

It is unclear—and the committee concludes that it is indeterminable, given current information—whether the 510(k) process over the last 35 years has had a positive or negative effect on innovation. To answer this question, the FDA should commission an assessment to determine this effect.

The Medical Device Regulatory System

The 510(k) process does not operate in isolation. Premarket review, including the 510(k) process, and postmarket oversight—from product labeling regulations to the reporting of adverse events associated with use of a device—make up a comprehensive medical device regulatory system. All the components of the system need to be functioning well in order to provide a reasonable assurance of the safety and effectiveness of medical devices.

The committee concludes that the 510(k) process lacks the legal basis to be a reliable premarket screen of the safety and effectiveness of moderate-risk devices and, furthermore, that it cannot be transformed into one.

No premarket regulatory system for medical devices can guarantee that all new medical devices will be completely safe and effective when they reach the market. Robust postmarketing surveillance is essential. The committee identified substantial problems in the current postmarketing surveillance of devices. The FDA should develop and implement a comprehensive strategy to collect, analyze, and act on medical device aftermarket performance information.

It is important for the FDA to use postmarket enforcement tools, such as seizing or banning a device, when necessary. The FDA has stated that there are limitations to the use of these tools but has not identified the limitations. The agency should review its postmarket regulatory powers to identify these limitations and address them.

The committee recommends that the FDA develop and implement a program of continuous quality improvement to increase predictability, transparency, and consistency in all regulatory decisions for devices and to address emerging issues that affect decision making.

Moving Forward

The committee finds that the current 510(k) process is flawed based on its legislative foundation. Rather than continuing to modify the 35-year-old 510(k) process, the committee concludes that the FDA's finite resources would be better invested in developing an integrated premarket and postmarket regulatory framework that provides a reasonable assurance of safety and effectiveness throughout the device life cycle. This new framework should:

- be based on sound science;
- be clear, predictable, straightforward, and fair;
- be self-sustaining and self-improving;
- facilitate innovation that improves public health by making medical devices available in a timely manner and ensuring their safety and effectiveness throughout their lifecycle;
- use relevant and appropriate regulatory authorities and standards throughout the life cycle of devices to ensure safety and effectiveness; and
- be risk-based.

Current information is not adequate to design a new framework, and the FDA should begin to obtain the needed information. Once adequate information is available to design an appropriate medical-device regulatory framework, Congress should enact legislation to do so. A new regulatory framework will benefit everyone—patients, healthcare providers, the medical device industry, payers, and the FDA.

INSTITUTE OF MEDICINE
OF THE NATIONAL ACADEMIES

Advising the nation • Improving health

500 Fifth Street, NW
Washington, DC 20001
TEL 202.334.2352
FAX 202.334.1412

www.iom.edu

The Institute of Medicine serves as adviser to the nation to improve health. Established in 1970 under the charter of the National Academy of Sciences, the Institute of Medicine provides independent, objective, evidence-based advice to policy makers, health professionals, the private sector, and the public.

別添 2. ICD safety, presentation at AHA

ICD Safety

Postmarketing Surveillance of Drugs and Devices

American Heart Association

Orlando

November 15, 2011

A Mother's report to the FDA

"My son was driving his car and passed out. He expired [in] 2010. Defibrillator failed to deliver shock due to broken lead. In 2004, the leads broke and were replaced. This is the second time the leads broke due to corrosion. There is no warning to let pt know leads have broken. Mfr is not accepting responsibility for their broken equipment. I have no recourse. I didn't even know the old leads were left inside my son's body. No one will help me and no one cares to take my case. If my son was hung by a toy there would be recourse. Toy mfrs are more liable."

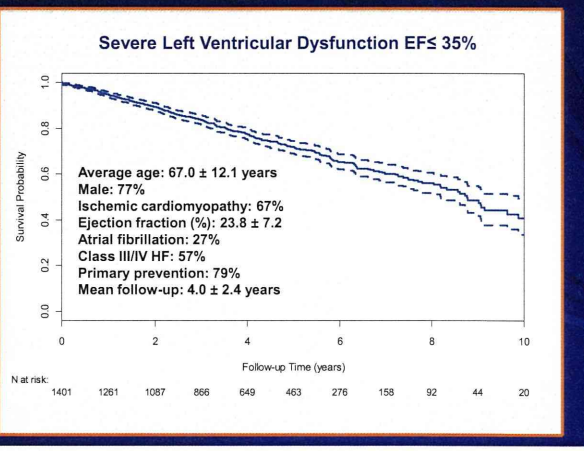
MDR event 1745477

Post-market Surveillance

- The goal of post-market surveillance is to enhance the public health by reducing the incidence of medical device adverse experiences.
- However, medical device surveillance in the United States depends largely on voluntary reporting of adverse events, and consequently early safety signals may be missed.
- This has resulted in a reactive surveillance system that fails to detect significant device defects before large patient populations are exposed to potentially hazardous products
- Further, as the result of the Supreme Court's ruling in Riegel v Medtronic, medical device companies are immunized from state court common-law claims involving products approved by the FDA.

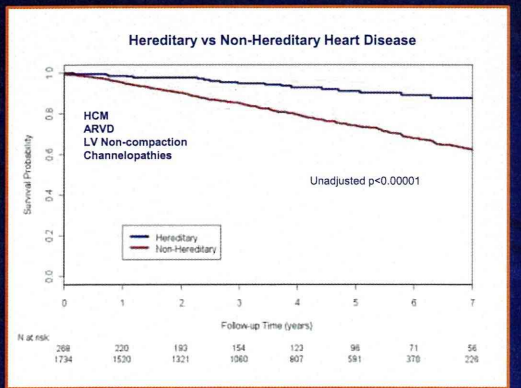
ICD Patient Survival 2000-2010

Minneapolis Heart Institute



ICD Patient Survival 2000-2010

Minneapolis Heart Institute



Evolution of ICD Pulse Generators

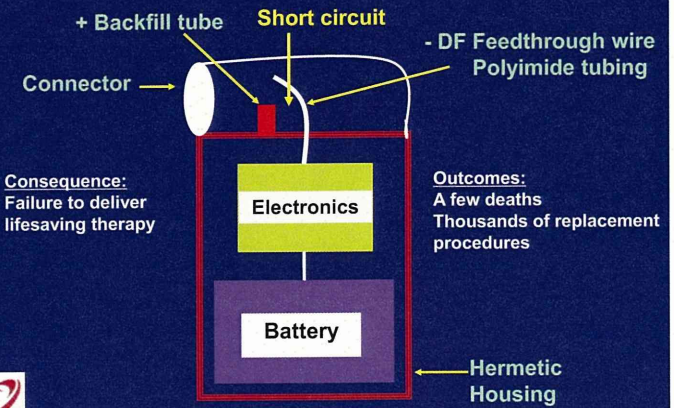
1986 to 2010

30J Shocks
No pacing
Non-programmable
Thoracotomy

Dual chamber
Pacing & sensing
Rate Response
Antitachycardia
Cardioversion
Hi-energy shocks
Diagnostics
Remote monitoring
Transvenous

Hauser R, Card Electrophysiol Clin 2009

Guidant Prizm 2 DR Failure

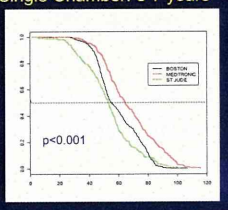


Consequence:
Failure to deliver lifesaving therapy

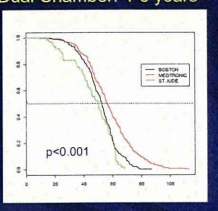
Outcomes:
A few deaths
Thousands of replacement procedures

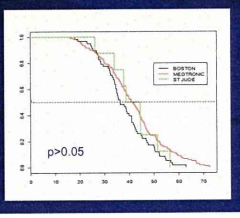
ICD Battery Longevity

Single Chamber: 5-7 years



Dual Chamber: 4-6 years





ICD-CRT: 3-4 years

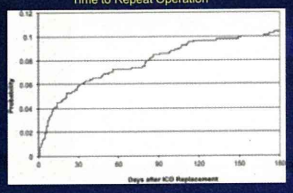
Kallinen L: European Society of Cardiology, Barcelona 2009

Surgical Complications After ICD Replacement

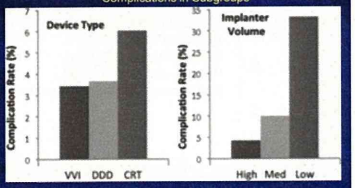
Ontario ICD Database

Overall 45-day complication rate in 1081 patients undergoing ICD replacement was 4.3%, including infection (2.1%) and lead revision (3.2%).
"Generator change is a higher risk procedure than new implants, which argues for developing longer-lived devices……"

Time to Repeat Operation



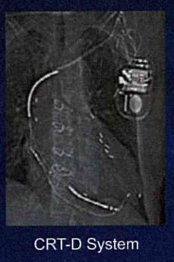
Complications in Subgroups



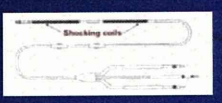
Krahn A D et al. Circ Arrhythm Electrophysiol 2011;4:136-142

"Leads have been the Achilles heel of ICD therapy"

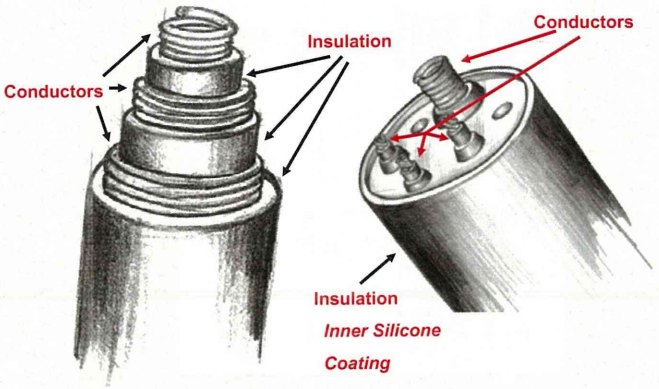
Multiple authors 1989-2010



CRT-D System



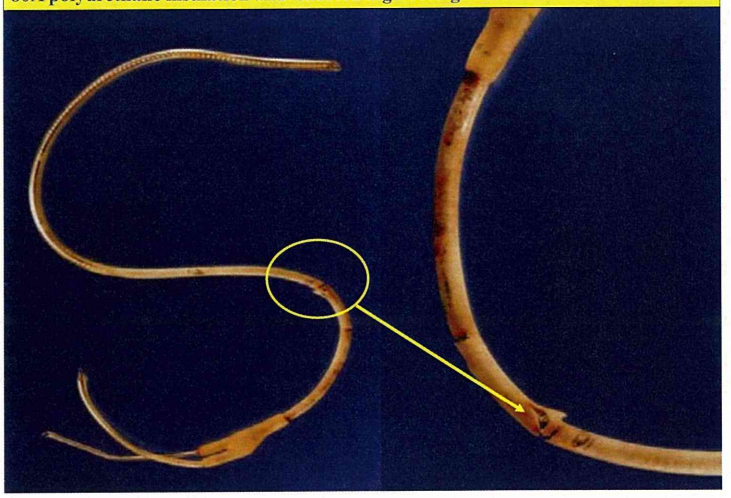
ICD Lead Designs



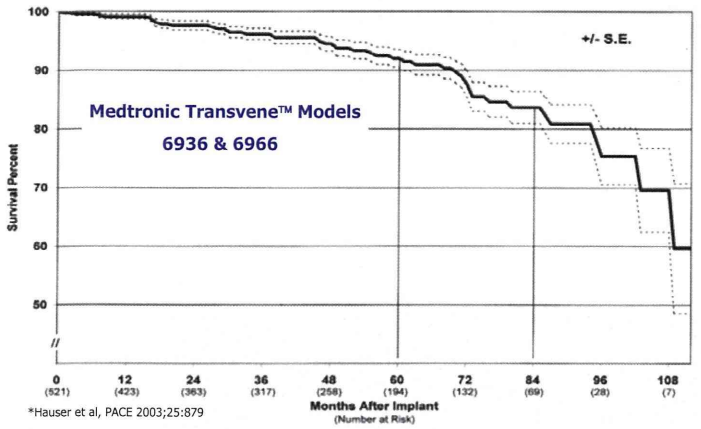
Coaxial Polyurethane

Multilumen Silicone

Failed Transvene model 6966 ICD lead after extraction showing disrupted outer 80A polyurethane insulation and shorted high voltage coil.

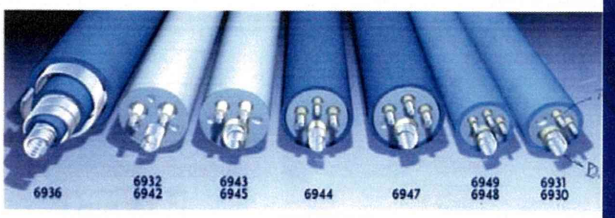


Survival of Coaxial Polyurethane Leads*



*Hauser et al, PACE 2003;25:879

Coaxial design was abandoned. Multilumen construction focused on reducing lead diameter

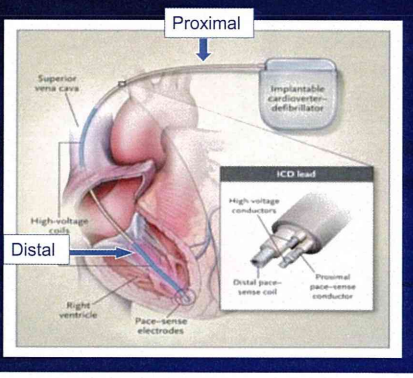


Market Release	1993	1996/97	1997/98	2000	2001	2004
	10 Fr.		7.8 Fr.		8.2 Fr.	6.6 Fr.

Sprint Fidelis ICD Lead

- Small diameter 6.6 French
- Silicone insulation
- In 2004 FDA approved with no clinical testing or human safety data.
- Rapidly became the most popular ICD lead ever marketed with monthly sales of ≈ 7,000 leads, which were implanted in patients at risk for sudden cardiac death.

In January 2007 we recognized that the Sprint Fidelis ICD lead was prone to fracture. The primary sign of failure was multiple inappropriate high voltage shocks.



Early Failure of Sprint Fidelis Small Diameter ICD Leads

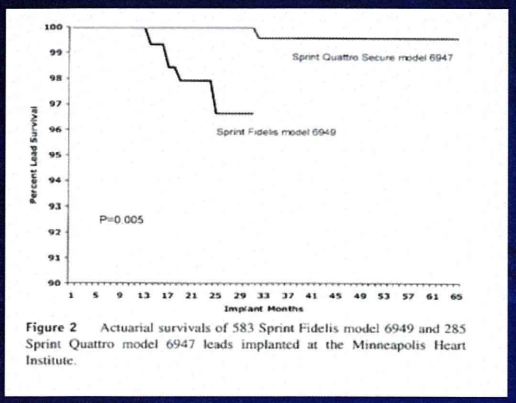
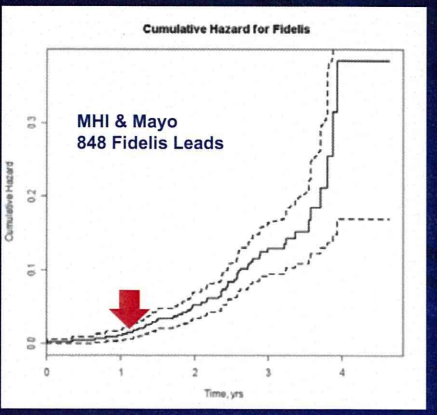


Figure 2 Actuarial survivals of 583 Sprint Fidelis model 6949 and 285 Sprint Quattro model 6947 leads implanted at the Minneapolis Heart Institute.

Hauser et al, Heart Rhythm 2007; 4:892

Accelerating Fidelis Failure



Hauser & Hayes, Heart Rhythm 2009; 6:605-610

Lead Integrity Alert (LIA)

Triggers

High Impedance

OR

Rapid Oversensing
Sensing Integrity Counter ≥ 30 in 3 days
and
Two Non-Sustained Tachycardias <220 ms

Response

Notifications

At least 6x/day

Patients

Audible tone

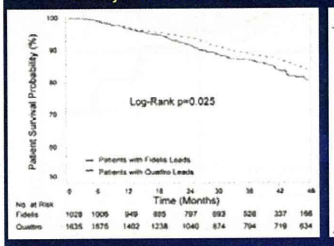
Automatic Δ VF Detection

↑ VF NID to 30/40

Swerdlow et al, Circulation 2008; 118: 2122-2129
Kallinen et al, Heart Rhythm 2010; 7: 1048-1055

Increased Mortality in Fidelis Patients?

Unadjusted Survival



Multivariate Predictors of Mortality

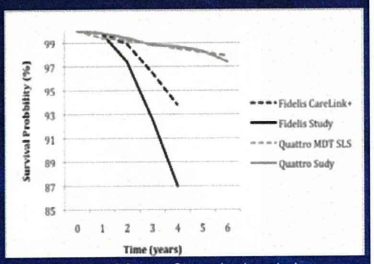
	Hazard Ratio (95% CI)	p Value
Lead type (Fidelis vs. Quattro)	1.056 (0.84–1.33)	0.6353
ICD indication (secondary vs. primary)	1.380 (1.08–1.76)	0.0097
Atrial lead	1.409 (1.10–1.81)	0.0077
Heart failure	1.611 (1.21–2.14)	0.001
Number of generator replacements	0.310 (0.24–0.41)	<0.0001
Age (per 1-yr increase)	1.036 (1.026–1.05)	<0.0001
History of peripheral arterial disease	1.529 (1.18–1.99)	0.0016
Ejection fraction (per 1% increase)	0.978 (0.968–0.99)	<0.0001
Atrial fibrillation	1.609 (1.31–1.98)	<0.0001
Chronic dialysis	3.298 (2.19–4.97)	<0.0001
Chronic obstructive pulmonary disease	1.372 (1.08–1.75)	0.0108

Morrison et al, JACC 2011; 58: 278-83

Risk Factors for Fidelis Failure

Multivariate analysis of clinical variables associated with Fidelis lead failure.

Variable	P value	Hazard Ratio (95% bounds)	Comment
Age	P=0.007	0.977 (0.961,0.994)	Younger patients at higher risk
Male	P=0.048	0.614 (0.379,0.995)	Female patients at higher risk
Cardiac disease	P=0.04		Hazard ratios are relative to dilated cardiomyopathy
Hypertrophic Cardiomyopathy		3.664 (1.616,8.306)	
ARVD & channelopathies		2.498 (0.907,6.875)	
Ischemic Heart Disease		2.082 (1.113,3.893)	
Idiopathic VT/VF		1.971 (0.447,8.696)	



Sprint Fidelis and Quattro Secure lead survival probabilities from this study and Medtronic's post-market CareLink PLUS (+) study

Hauser et al, Circulation 2011; 123: 358-363

Is it possible to detect potentially defective leads before large patient populations are exposed?

- Automated
  - Timely detection of post-market product issues
- Analytic capabilities
  - Assess low-frequency events
  - Track accumulating experiences
  - Monitor multiple data sets
- Large registries and databases
  - Statistical power
- Data Extraction and Longitudinal Trend Analysis (DELTA)
- Validated on clinical and outcomes databases
- Statistical methods
  - Bayesian
  - Propensity scoring
  - Survival analysis
- Applicable to large registries and databases

We Hypothesized that…

- DELTA would have identified the Sprint Fidelis problem earlier than existing post-market surveillance methods, and well before it was recalled by the manufacturer.
- By implication DELTA would have prevented thousands of Fidelis implants and the adverse events, including surgical revision, caused by Fidelis failures.

Methods

- We retrospectively applied DELTA to our multicenter database of 1,038 Fidelis leads and 1,668 Quattro Secure leads, which served as the control.
- The DELTA analysis recreated Fidelis survival data as they would have existed at monthly intervals and compared them to similar data for the Quattro control lead.
- The Mantel-Cox log-rank test compared Fidelis and Quattro survivals. The DELTA alert was set to trigger when the log rank p-value was <0.05.