US Evaluation of DuraGraft®

DuraGraft – For the Prevention of Vascular Graft Disease and to Reduce the Incidence of Clinical Complications of Graft Failure

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1 Introduction

1.1 Coronary Artery Disease and Coronary Artery Bypass Graft (CABG) Surgery

An estimated 15.5 million patients in the United States have Coronary Artery Disease (CAD), a debilitating and often deadly disease. Each year, 1.5 million individuals with CAD suffer an acute Myocardial Infarction (MI) and about 600,000 of those patients die. CABG is the last resort treatment for many CAD patients.

To address the medical need that CAD presents, drugs, devices, and procedures, all with unique risks and benefits have been developed to detect, manage, treat and/or prevent the disease. Practice guidelines related to the use of these products and procedures have been jointly created by the American College of Cardiology Foundation (ACCF) and the American Heart Association (AHA). Specific guidelines for Coronary Artery Bypass Graft Surgery (CABG), the surgical procedure used to bypass coronary artery blockages and restore blood flow to the heart were also drafted by the ACCF/AHA task force. According to these guidelines, CABG is the only treatment option for many patients and is the preferred treatment for many other patients. Approximately 400,000 procedures are performed annually in the US alone. [1]

Multiple native vessels are bypassed in most CABG surgeries, and autologous saphenous vein grafts are used in 85% of CABG surgeries worldwide. Unfortunately, the durability and patency of bypass grafts are significantly compromised by Vein Graft Disease (VGD) in a process that begins during the CABG surgery itself. VGD is the principal cause of both early (within 30 days) and intermediate/late vein graft failure.

1.2 CABG Surgery and Vein Graft Failure

While CABG inarguably saves lives, 12-month vein graft failure (VGF) rates remain unacceptably high, predisposing the patient to death, MI and the need for re-intervention. The PREVENT IV study carried out by the Duke Clinical Research Institute (DCRI), the largest prospective study to evaluate VGF post-CABG, found the angiographic 12-month patient-level VGF rate to be 46% and the graft-level VGF rate to be 29%.[2] Recent sub-analyses of this data by DCRI demonstrated that amongst the dozens of factors evaluated, few factors were found to correlate with the subsequent development of VGF, and these factors were almost exclusively due to intraoperative damage that occurred primarily during the ischemic storage period.[3,4]

The intraoperative damage that occurs to vein grafts triggers the progressive process of VGD that encompasses the pathophysiological changes that occur in vein grafts following their use in surgical grafting. As VGD progresses, vein grafts lose their ability to adapt to the post-grafting environment leading to thrombus formation, intimal hyperplasia and atherosclerosis. VGD that progresses to VGF may result in death, myocardial infarction, the need for repeat revascularization and poorer quality of life. Since the success rate of re-intervention of a failed graft is poor, addressing early vein graft disease in the primary graft is crucial.[5]

1.3 Clinical Evaluation of DuraGraft® Overview

DuraGraft is a one-time intraoperative treatment designed to prevent vascular graft disease and graft failure and reduce the clinical complications associated with graft failure.

A large retrospective study of over 2400 patients has shown the benefit of intraoperative DuraGraft treatment on both short and long term clinical outcomes in patients undergoing CABG surgery at the Boston VA Medical Center when compared to patients receiving no treatment. Data was collected from 2436 patients between the ages of 18-90 undergoing CABG surgery with at least one vein graft. The main exposure variable was intraoperative treatment with DuraGraft. No vein treatment was used between 1996-1999, while DuraGraft vein treatment was used exclusively between 2001-2004. Therefore, exposure groups were defined based on date of initial CABG surgery.

Multiple short-term and long-term outcomes events were examined. Short-term outcomes were defined as events occurring within 30 days of surgery. Long-term outcomes were defined as events occurring after 30 days and included major adverse cardiovascular events (MACE), repeat revascularization (CABG/PCI), non-fatal MI and death.

Propensity matching was performed and data analysis was performed as a crude analysis on all patients as well as with only subjects included in the IPW adjusted models and finally as an IPW adjusted analysis. Cox proportional hazards regression analyses were performed to examine the association between DuraGraft treatment and 5-year outcomes. Data past five years was also collected and is presented in this paper.

The intraoperative treatment of grafts with DuraGraft as compared to untreated grafts was shown to be associated with highly and statistically significant reductions in complications associated with VGF (non-fatal MI, repeat revascularization, and MACE) over five years. Further significant improvements were also observed post five years indicating that intraoperative treatment of veins with DuraGraft provides short- and long-term benefits to the patient. This study represents any notable improvement for clinical outcomes following CABG surgery for the first time in CABG history.

1.4 Human Clinical Investigations

Methods, Results and Discussion

The VA-Roxbury Study is an independent Physician Investigator (PI) initiated, single-center, multi-surgeon, retrospective, comparative clinical trial conducted to assess the safety and impact of DuraGraft® treatment on both short and long-term clinical outcomes in patients who underwent CABG with saphenous vein grafts (SVGs) at the Boston VA Medical Center. The time interval (1996-1999) selected for this analysis represents a time period when vein graft treatment was not available during CABG surgery and a time period after the center changed to exclusively intraoperatively treating grafts with DuraGraft (2001-2004). Year 2000 was omitted from this analysis by the PI due to the transition of the implementation of DuraGraft treatment into the clinic and the uncertainty of its use in CABG patients during the transition period.

Data was extracted from a total of 2,436 patients who underwent a CABG procedure with at least one SVG from 1996-1999 (No Treatment n=1,400 pts.) and 2001-2004 (DuraGraft Treatment n=1,036 pts.). The median age was 65 for the No Treatment group and 66 for the DuraGraft group. Patient demographics are shown below (**Table: 1**). Patients were excluded from the study if they had a prior history of CABG, had no use of SVG, or underwent additional procedures during the CABG surgery. Propensity scores were calculated with a multivariate logistics regression model using DuraGraft exposure as the outcome and any potential confounders as predictors. Inverse Probability Weights (IPWs) were calculated as the inverse probability of the treatment received using propensity scores. For each outcome, a crude analysis with all subjects (2436), a crude analysis with only subjects included in the IPW adjusted models (2065), and an IPW adjusted analysis (2065) were conducted. The two crude analyses were performed to evaluate any potential bias that might be caused by missing informative data.

Based on limited data availability prior to the year 2000 and because data did not fit the Cox Proportional Hazards assumption, long-term analyses were performed starting at 1000 days post CABG. This does not mean however that there were no effects prior to 1000 days; only that analysis is difficult at earlier times for the reasons stated. Where possible< 30 day data is also shown.

Table 1: Patient demographics for this study

	Demographic	No Treatment	Treatment	P-Value
Gender*	Male	1383 (99.00%)	1029 (99.32%)	0.3894
	Female	14 (1.00%)	7 (0.68%)	
Age	(Years)	65.80±9.66	66.74±9.55	0.0182
Race**	White	1335 (96.04%)	996 (94.89%)	0.2258
	Black	31 (2.23%)	24 (2.36%)	
	Other	24 (1.73%)	28 (2.75%)	
Ethnicity***	Hispanic/Latino	7 (0.85%)	8 (0.92%)	0.8795
	Not Hispanic/Latino	818 (99.15%)	864 (99.08%)	

*3 Missing Values; **28 Missing Values; ***739 Missing Values

1.4.1 Long-term Results Evaluating Non-Fatal MI

Starting from 1000-days post-CABG, the data demonstrates that DuraGraft® Treatment as compared to No Treatment had protective effects and statistically significantly reduced the rate of non-fatal MI.

Both crude and IPW adjusted analyses demonstrate that DuraGraft is significantly associated with decreased likelihood of non-fatal acute MI as compared to No Treatment starting at 1,000 days after CABG surgery through five years post-CABG. The crude analysis demonstrated a statistically significant 47% reduced risk of a non-fatal MI while the IPW adjusted analysis demonstrated a statistically significant 50% reduction in risk (crude HR, 0.527; 95% CI: 0.425, 0.653; p = <.0001 /adjusted HR, 0.496; 95% CI: 0.348, 0.707; p = 0.0001) (**Table: 2, Figure: 1)**. The Cox regression analysis also shows that DuraGraft has continued benefit past five years in that the rate of non-fatal MI continues to be further reduced through at least 12 years post-CABG implying that DuraGraft has extended long-term benefits for the patient **(Figure: 1)**.

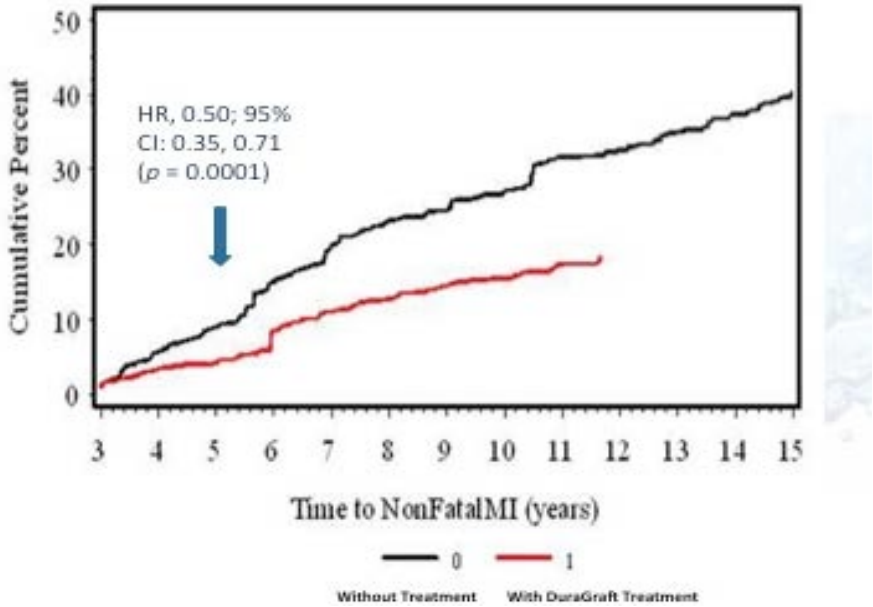
It is interesting to note that despite the limitations with data analysis prior to 1000 days-post CABG, non-fatal MI was still observed to be significantly reduced in patients receiving DuraGraft treatment when analysis starts at 30-days post-CABG **(Table: 2)**. The crude model shows that subjects who received DuraGraft had a statistically significant 31% reduction in the rate of non-fatal MI as compared to patients who received no treatment (HR: 0.687, 95% CI: 0.585, 0.806; p = <.0001). After adjusting for IPWs, subjects who received DuraGraft also showed a statistically

significant 36% reduction in the rate of non-fatal acute MI as compared to those who received No Treatment (95% CI: 0.499, 0.8154; p = 0.0003).

Table 2: Long-Term Non-Fatal Acute MI

Outcome	Start (days post CABG)	Model	Hazard Ratio	Lower CI	Upper CI	P-Value
Non-fatal Acute MI	1,000	Crude, All Subjects	0.527	0.425	0.653	<0.0001
Non-fatal Acute MI	1,000	IPW Adjusted	0.496	0.348	0.707	0.0001
Non-fatal Acute MI	>30	Crude, All Subjects	0.687	0.585	0.806	<0.0001
Non-fatal Acute MI	>30	IPW Adjusted	0.637	0.499	0.814	0.0003

Figure 1: IPW Adjusted Cumulative Incidence for Non-Fatal MI from 1000 Days Post CABG



1.4.2. Long-term Results Evaluating Revascularization

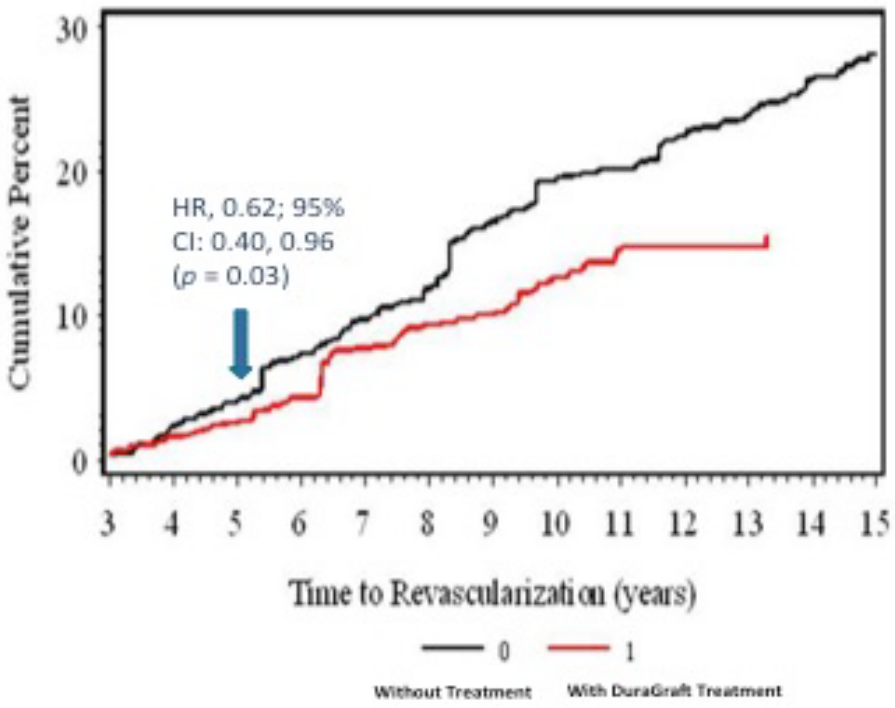
Starting from 1000 days-post CABG, the data demonstrates that DuraGraft® Treatment as compared to No Treatment had protective effects in that the rate of repeat revascularization is significantly reduced in the DuraGraft treatment group. Both crude and IPW adjusted models show that DuraGraft is significantly associated with decreased likelihood of repeat revascularization starting at 1,000 days post-CABG through five years as compared to No Treatment. The crude analysis demonstrates a statistically significant 35% reduced risk of repeat revascularization while the IPW adjusted analysis demonstrated a statistically significant 38.5% reduced risk of repeat revascularization (crude HR, 0.651; 95% CI: 0.509, 0.833; p = 0.0006 /IPW adjusted HR, 0.625; 95% CI: 0.404, 0.955; p = 0.0300) (**Table: 2, Figure: 2**).

Table 2: Long-Term Repeat Revascularization

Outcome	Start (days post CABG)	Model	Hazard Ratio	Lower CI	Upper CI	P-Value
Repeat Revascularization	1,000	Crude, All Subjects	0.651	0.509	0.833	0.0006
Repeat Revascularization	1,000	IPW Adjusted	0.622	0.404	0.955	0.0300

The Cox regression analysis also shows that DuraGraft® has continued benefit past five years in that the rate of repeat revascularization continues to be reduced through at least 12 years post-CABG implying that DuraGraft has extended long-term benefit for the patient **(Figure: 2)**.

Figure 2: IPW Adjusted Cumulative Incidence of Revascularization from 1000 Days Post CABG



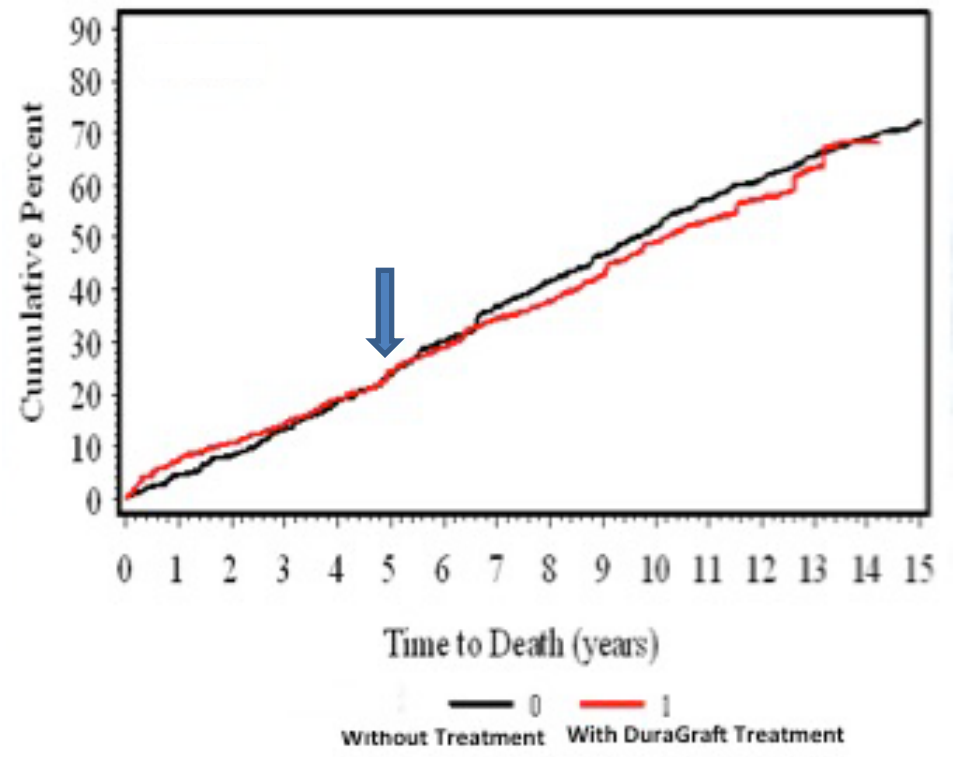
1.4.3 Long-term Results Evaluating Death

Both crude and IPW adjusted models demonstrate that DuraGraft® was not significantly associated with an increased likelihood of "all cause death" after beginning 30 days or 1,000 days post-CABG surgery through five years post-CABG as compared to No Treatment (crude HR, 0.922; 95% CI: 0.820, 1.037; *p* = 0.1765/ adjusted HR, 0.906; 95% CI: 0.755, 1.088; *p* = 0.2907) Data shown only for beginning 30 days after CABG surgery (**Table: 3, Figure: 3**). Therefore, the use of DuraGraft in CABG surgery does not influence the likelihood of all-cause death as these events occurred with similar frequency in both the DuraGraft treatment and the untreated groups.

Table 3: Long-Term All Cause Death

Outcome	Start (days post CABG)	Model	Hazard Ratio	Lower CI	Upper CI	P-Value
Death	1,000	Crude, All Subjects	0.922	0.820	1.037	0.1765
Death	1,000	IPW Adjusted	0.906	0.755	1.088	0. 2907

Figure 3: IPW Adjusted Cumulative Incidence for Death from 30 Days Post CABG



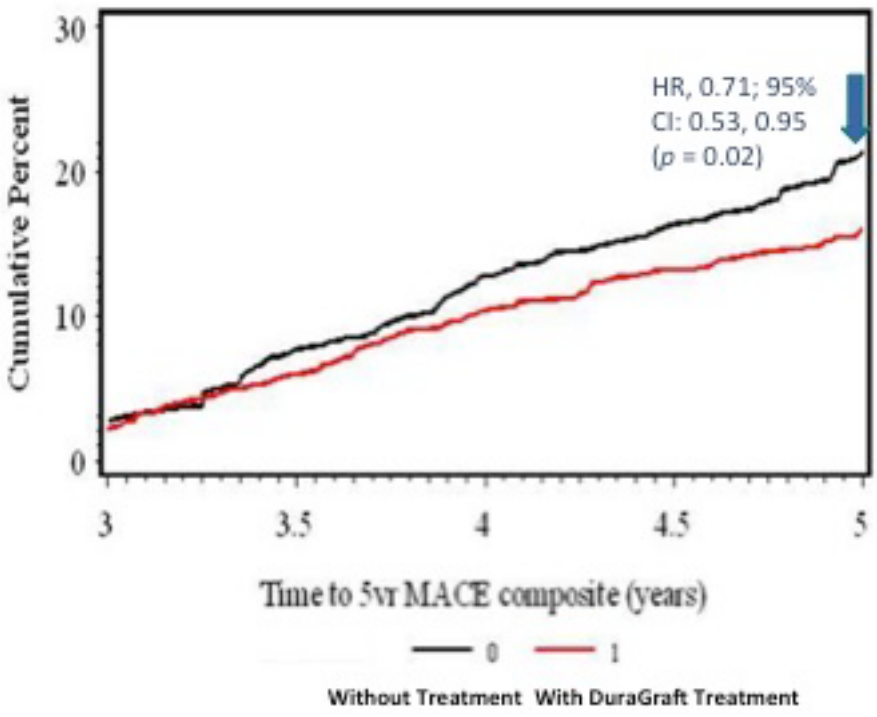
1.4.4. Long-term Results Evaluating MACE

Starting at 1000 days post CABG, the data demonstrates that DuraGraft® Treatment as compared to No Treatment reduced the incidence of MACE composite events. Both crude and IPW adjusted models demonstrate that DuraGraft is significantly associated with decreased likelihood of the occurrence of MACE starting at 1,000 days post-CABG surgery through five years post-CABG as compared to No Treatment (crude HR, 0.751; 95% CI: 0.611, 0.923; p = 0.0065/ adjusted HR, 0.707; 95% CI: 0.525, 0.952; p = 0.022) (**Table: 4, Figure: 4)**. The reduction in MACE was driven by the reduction in both non-fatal MI and repeat revascularization.

Table 4: Long-Term MACE

Outcome	Start (days post CABG)	Model	Hazard Ratio	Lower CI	Upper CI	P-Value
MACE	1,000	Crude, All Subjects	0.751	0.611	0.923	0.0065
MACE	1,000	IPW Adjusted	0.707	0.525	0.952	0.022

Figure 4: IPW Adjusted Cumulative Incidence for 5 Year MACE from 1000 Days Post CABG



1.4.5. Short-term Results (30 days post CABG)

A small number of outcome events occurred during the 30 day follow-up period. The frequencies of short-term outcome events for each group are presented below (**Table: 5**).

Table 5: Frequency of Short-Term Outcomes by Treatment Group

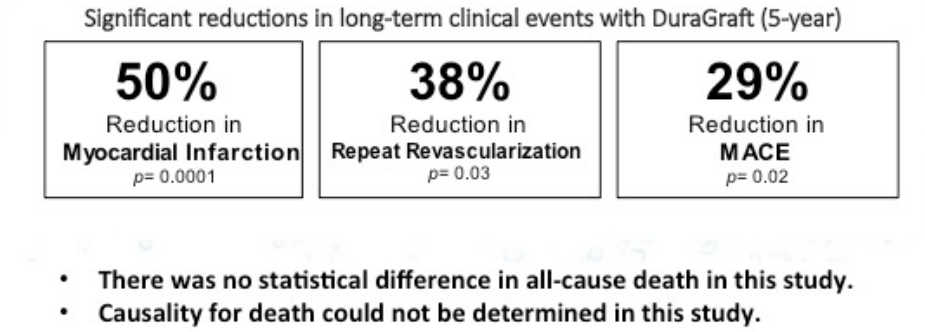
Events	No Treatment (n=1400) Events (%)	DuraGraft® Treatment (n=1036) Events (%)	P-Value Crude, All Subjects
Any Event	89 (6.4%)	60 (5.8 %)	NS
Perioperative MI	29 (2.0%)	5 (0.5%)	0.002
>48 Hour Ventilation	57 (4.0%)	47 (4.5%)	NS
Coma	4 (0.3%)	6 (0.6%)	NS
Renal Failure	8 (0.6%)	5 (0.5%)	NS
Death	20 (1.4%)	21 (2.0%)	NS

Perioperative MI was significantly reduced by 25% in the DuraGraft group as compared to patients in the control group (**Table: 5).**

1.4.6 Conclusion

The data presented here in a study that comprised of 2400+ US patients supports not only safety but also improved short and long-term clinical outcomes in DuraGraft® treated CABG patients. **Figure 5** summarizes the reduction in rates of MACE and MACE composite endpoints in DuraGraft treated CABG patients. It is of note to point out that the statistically significant reductions in these serious adverse events are consistent with trends observed in a smaller retrospective study pilot conducted in the EU to evaluate DuraGraft safety and performance (data not shown).

Figure 5: Summary of Clinical Outcomes



- **There was no statistical difference in all-cause death in this study.**
- **Causality for death could not be determined in this study.**

1.4.7 Study Limitations

Certain limitations are inherent in a retrospective study of this nature. While this study provides foundational evidence supporting the use of DuraGraft® as an ideal treatment option for vascular grafts, the limitations, while challenging, cannot be overlooked. The limitations of this study included the following: secular trends for operating on less healthy patients, differences in how patients were selected over time, variation in how patients were treated over time, the treatment and non-treatment groups were not concurrent and there was paucity of data requiring the adjustment to 1000 days on due to missing follow-up data occurring during 1996-1999. Despite these limitations, the strengths of the study are in its evaluation of a large patient population that captures true clinical practice evidence, strong IPW matching, follow-up comparisons up to 14 years and high concordance between the three analyses: two crude and one IPW adjusted. Although this study is retrospective, Ferguson and Chen[6] conclude that "randomized controlled trial data parallel the findings of observational studies in MACE outcomes of CABG patients. This data synergy has changed the information matrix for decision-making in Stable Ischemic Heart Disease (SIHD) revascularization."

2 Summary and Conclusions

While CABG inarguably saves lives, VGF predisposes the patient to myocardial infarction and re-intervention. Diminished circulation to the heart muscle has significant consequences, and these include not only debilitating MACE events but also repeat hospitalization and physician visits requiring other medical interventions, medications, rehabilitation, diminished quality of life and possibly deleterious effects on other organ systems such as the nervous system (cerebrum) and kidney. The CABG procedure as it is practiced today with no vein graft treatment is substantially and negatively impacted by high VGF rates that are routinely observed. These VGF rates have largely remained unchanged since CABG was introduced as a treatment for CAD 60 years ago.

The correlation between graft failure and adverse outcomes is known to exist; "bypass graft failure (CABG) has been shown in a number of studies to be independently correlated with a variety of adverse clinical outcomes including death, myocardial infarction, revascularization, and worsening of symptoms such as angina."[7, 8] "Early Vein Graft Failure is associated with worse long term outcomes after CABG", and "non-occlusive VGF was the strongest predictor of the composite outcome (following CABG) of death, MI and revascularization".[8]

2.1 Vein Graft Disease and Vein Graft Failure are Preventable

DuraGraft®, a one-time intraoperative treatment designed to prevent vascular graft disease and failure has been shown to reduce with statistical significance the incidence of clinical complications following coronary bypass surgery by addressing vascular endothelial damage that occurs intra and peri-operatively. DuraGraft is an ionically balanced and buffered treatment containing antioxidants that prevents damage to vascular grafts and supports the production of nitric oxide, and thus protects the associated endothelium during *ex vivo* intraoperative procedures. The treatment is provided in a ready-to-use formulation for use intraoperatively and is compatible with current surgical practices.

3 REFERENCES

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