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CENTERS FOR MEDICARE AND MEDICAID SERVICES
MEDICARE EVIDENCE DEVELOPMENT & COVERAGE ADVISORY
COMMITTEE

JULY 18, 2007

CENTERS FOR MEDICARE AND MEDICAID SERVICES
7500 SECURITY BOULEVARD
BALTIMORE, MARYLAND

PANELISTS

CHAIRPERSON
ALAN M. GARBER, M.D., PH.D.

VICE-CHAIR
ALEXANDER H. KRIST, M.D.

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CAROLE REDDING FLAMM, M.D., M.P.H.
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WILLIAM H. MAISEL, M.D., M.P.H.
BARRY D. PRESSMAN, M.D.
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MARK SLAUGHTER, M.D.

HCFA LIAISON
STEVE E. PHURROUGH, M.D., M.P.A.
MARCEL SALIVE, M.D.

PANELISTS (CONTINUED)

CONSUMER REPRESENTATIVE
LINDA A. BERGTHOLD, PH.D.

INDUSTRY REPRESENTATIVE
MICHAEL J. LACEY, M.SC.

GUEST EXPERT PANELISTS
MATTHEW S. EDWARDS, M.D.
STEPHEN C. TEXTOR, M.D.

EXECUTIVE SECRETARY
MICHELLE ATKINSON

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PANEL PROCEEDINGS

(THE MEETING WAS CALLED TO ORDER AT 8:05 A.M., WEDNESDAY, JULY 18, 2007.)

MS. ATKINSON: GOOD MORNING AND WELCOME COMMITTEE CHAIRPERSON, MEMBERS AND GUESTS. I AM MICHELLE ATKINSON, THE EXECUTIVE SECRETARY FOR THE MEDICARE EVIDENCE DEVELOPMENT AND ADVISORY COMMITTEE. THE COMMITTEE IS HERE TODAY TO DISCUSS THE EVIDENCE, HEAR PRESENTATIONS AND PUBLIC COMMENT, AND MAKE RECOMMENDATIONS CONCERNING PERCUTANEOUS TRANSLUMINAL ANGIOPLASTY AND STENTING OF RENAL ARTERIES.

THE FOLLOWING ANNOUNCEMENT ADDRESSES CONFLICT OF INTEREST ISSUES ASSOCIATED WITH THIS MEETING AND IS MADE PART OF THE RECORD. THE CONFLICT OF INTEREST STATUTES PROHIBIT SPECIAL GOVERNMENT EMPLOYEES FROM PARTICIPATING IN MATTERS THAT COULD AFFECT THEIR OR THEIR EMPLOYER'S FINANCIAL INTERESTS. EACH MEMBER WILL BE ASKED TO DISCLOSE ANY FINANCIAL CONFLICTS OF INTEREST DURING THEIR INTRODUCTION.

WE ASK IN THE INTEREST OF FAIRNESS THAT ALL PERSONS MAKING STATEMENTS OR PRESENTATIONS ALSO DISCLOSE ANY CURRENT OR PREVIOUS FINANCIAL INVOLVEMENT IN ANY COMPANY THAT MANUFACTURES DEVICES FOR RENAL ARTERY STENTING OR SURGERY FOR THE TREATMENT OF RENAL ARTERY STENOSIS, DRUGS OR

BIOLOGICS USED IN THE TREATMENT OF RENAL ARTERY STENOSIS, OR OTHER TOOLS USED FOR DIAGNOSIS OR TREATMENT OF RENAL ARTERY STENOSIS. THIS INCLUDES DIRECT FINANCIAL INVESTMENTS, CONSULTING FEES AND SIGNIFICANT INSTITUTIONAL SUPPORT. IF YOU HAVEN'T ALREADY RECEIVED A DISCLOSURE STATEMENT, THEY ARE AVAILABLE ON THE TABLE OUTSIDE OF THIS ROOM.

WE ASK THAT ALL PRESENTERS PLEASE ADHERE TO THEIR TIME LIMITS. WE HAVE NUMEROUS PRESENTERS TO HEAR FROM TODAY AND A VERY TIGHT AGENDA, AND, THEREFORE, CANNOT ALLOW FOR EXTRA TIME. THERE IS A TIMER AT THE PODIUM THAT YOU SHOULD FOLLOW. THE LIGHT WILL BEGIN FLASHING WHEN THERE ARE TWO MINUTES REMAINING AND THEN TURN RED WHEN YOUR TIME IS UP. PLEASE NOTE THAT THERE IS A CHAIR FOR THE NEXT SPEAKER, AND PLEASE PROCEED TO THAT CHAIR WHEN IT IS YOUR TURN.

FOR THE RECORD, VOTING MEMBERS PRESENT FOR TODAY'S MEETING ARE ALEX KRIST, CHAIM CHARYTAN, MARK FENDRICK, CAROLE FLAMM, WILLIAM LEWIS, WILLIAM MAISEL, BARRY PRESSMAN, SANDY SCHWARTZ, MARK SLAUGHTER. A QUORUM IS PRESENT AND NO ONE HAS BEEN RECUSED BECAUSE OF CONFLICTS OF INTEREST. THE ENTIRE PANEL, INCLUDING THE NONVOTING MEMBERS, WILL PARTICIPATE IN THE VOTING. THE VOTING SCORES WILL BE

AVAILABLE ON OUR WEB SITE FOLLOWING THE MEETING. TWO AVERAGES WILL BE CALCULATED, ONE FOR THE VOTING MEMBERS AND ONE FOR THE ENTIRE PANEL.

I ASK THAT ALL PANEL MEMBERS PLEASE SPEAK DIRECTLY INTO THE MIKES, AND YOU MAY HAVE TO MOVE YOUR MIKES SINCE WE HAVE TO SHARE. NOW I WOULD LIKE TO TURN THIS OVER TO DR. STEVE PHURROUGH.

DR. PHURROUGH: GOOD MORNING. I'M STEVE PHURROUGH, THE DIRECTOR OF THE COVERAGE AND ANALYSIS GROUP. LET ME THANK YOU FOR BEING PRESENT TODAY, AND PARTICULAR THANKS TO THE PANEL MEMBERS FOR AGREEING TO TAKE TIME OUT OF THEIR BUSY SCHEDULES TO BE PART OF THIS MEETING TODAY.

OUR GOAL TODAY IS TO DISCUSS THE EVIDENCE AROUND TREATMENT FOR RENAL ARTERY STENOSIS. WHILE WE DO HAVE A PARTICULAR NCD LOOKING AT RENAL ARTERY STENOSIS, THE GOAL OF THIS PARTICULAR MEETING IS NOT TO MAKE DECISIONS AROUND WHETHER WE SHOULD OR SHOULD NOT PAY FOR CERTAIN TREATMENTS. OUR GOAL TODAY IS TO DISCUSS WHAT'S THE EVIDENCE. THE PANEL'S TASK AND CHALLENGE IS TO FOCUS ON THAT PARTICULAR QUESTION. WE WILL TAKE THAT INFORMATION AND USE THAT IN OUR DELIBERATIVE PROCESS AS WE MAKE DECISIONS AROUND WHETHER WE SHOULD OR SHOULD NOT MAKE ANY NATIONAL COVERAGE DECISION AROUND THE VARIOUS

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TREATMENTS FOR ARTERIAL STENOSIS.
WE DO HAVE A HISTORY OF HAVING VERY
VIGOROUS AND HEALTHY DEBATES IN THESE PARTICULAR
MEETINGS. WE WANT THAT TO CONTINUE. WE WANT THE
MEETING TO FOCUS ON THOSE DEBATES, SO WE DO ENCOURAGE
THE PRESENTERS TO BE SUCCINCT, BRIEF AND TO THE
POINT, SO THAT WE CAN GET TO THE QUESTION AND ANSWER
TIME OF THE PROGRAM. THERE IS A LIMITED AMOUNT OF
TIME SO WE DO WANT TO BE FOCUSED ON SPECIFIC
QUESTIONS AND COMMENTS THAT ARE HELPFUL TO THE
DISCUSSION.
BEFORE I TURN IT OVER TO ALAN GARBER, I
WOULD LIKE TO MAKE A SPECIFIC NOTE TODAY THAT ALAN
GARBER HAS BEEN OUR CHAIRMAN FOR TWO YEARS. OUR
CHARTER ONLY ALLOWS A CHAIRMAN TO FUNCTION FOR TWO
YEARS, SO THIS IS ALAN'S LAST MEETING AS CHAIRMAN.
HE WILL CONTINUE TO BE A PANEL MEMBER BUT THIS IS HIS
LAST MEETING AS CHAIRMAN, AND I THANK HIM FOR THAT
SERVICE OVER THE LAST TWO YEARS.
THIS IS ALSO ALEX'S LAST MEETING AS VICE
CHAIRMAN. HOWEVER, HE HAS BEEN A PANEL MEMBER FOR
FOUR YEARS AND THAT'S THE LIMIT OF SERVING ON THE
PANEL, YOU HAVE TO TAKE A YEAR SABBATICAL BEFORE YOU
CAN BE RENOMINATED TO THE PANEL. SO NOT ONLY IS THIS
ALEX'S LAST MEETING AS VICE CHAIR, IT'S ALSO HIS LAST

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MEETING AS A PANEL MEMBER, AND WE WANT TO THANK ALEX FOR HIS WORK ON THE PANEL FOR THE LAST YEARS. AND FINALLY, BEFORE TURNING IT OVER TO ALAN, I MUST APOLOGIZE. I'M GOING TO HAVE TO BE OUT MOST OF THE DAY, A COUPLE OF CRITICAL ISSUES HAVE OCCURRED IN OUR ARENA THAT NEED TO BE RESOLVED TODAY AND TOMORROW. DR. SALIVE WILL BE SITTING IN IN MY PLACE WHEN I'M NOT HERE.

SO WITH THAT, I'LL TURN IT OVER TO ALAN.

DR. GARBER: THANK YOU, STEVE. GOOD MORNING, EVERYONE, AND WELCOME TO THE MEDICAL EVIDENCE DEVELOPMENT AND COVERAGE ADVISORY COMMITTEE MEETING. TODAY WE HAVE A SOMEWHAT PACKED SCHEDULE BUT ALSO I THINK A VERY INTRIGUING ONE, AND ONE THAT I THINK IS GOING TO BE VERY INTERESTING, AND I'M ANTICIPATING DISCUSSIONS AT A HIGH LEVEL. WE HAVE A GREAT SET OF PANELISTS, A GREAT SET OF SCHEDULED SPEAKERS. FROM THE MATERIALS WE HAVE BEEN SENT, I AT LEAST HAVE BEEN VERY GRATIFIED TO SEE HOW DIRECTLY THE COMMENTS ADDRESS THE QUESTIONS THAT WE ARE FACING TODAY.

STEVE MENTIONED THAT THIS IS MY LAST MEETING AS CHAIR OF MEDCAC AFTER TWO YEARS OF SERVICE. I WAS ALSO ON THE PREDECESSOR, MCAC, FROM ITS INCEPTION, AND IT HAS BEEN REALLY EXTRAORDINARY

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TO SEE HOW THIS PROCESS HAS GROWN AND IMPROVED AND BECOME BOTH FORMALIZED BUT ALSO MUCH MORE FOCUSED, AND I BELIEVE IN THE END EFFECTIVE. AND THE QUALITY OF THE DISCUSSION, THE QUALITY OF THE PANEL MEMBERS, THE QUALITY OF THE COMMENTS FROM THE PUBLIC HAS JUST IMPROVED STEADILY OVER TIME, AND I THINK THIS IS TESTIMONY TO THE CMS STAFF IN PARTICULAR, WHO'VE WORKED VERY HARD IN THIS AREA FOR A NUMBER OF YEARS. ANYBODY WHO WAS THERE AT THE BEGINNING KNOWS THAT THERE WAS A CERTAIN AMOUNT OF EXPERIMENTATION AND SORT OF FINDING YOUR WAY. THOSE DAYS ARE FAR BEHIND US NOW AND I THINK WE HAVE A VERY STRONG PROCESS THAT IS ADMIRED AROUND THE WORLD, ALTHOUGH NOT NECESSARILY ALWAYS PRAISED FOR ITS DECISIONS, OF COURSE, BUT THE FACT IS THAT THE DISCUSSION IS ONE THAT GENERALLY REALLY ADVANCES PEOPLE'S THINKING ABOUT THE ISSUES ON THE TABLE. I WANT TO JUST REINFORCE ONE THING THAT MICHELLE MENTIONED. BECAUSE WE'RE ON A TIGHT SCHEDULE, WE WILL BE VERY STRICT IN HAVING SPEAKERS LIMIT THEIR COMMENTS TO THE TIME ALLOTTED AND IN FACT WE HAVE CUT OFF SPEAKERS IN MID-SENTENCE. I APOLOGIZE IN ADVANCE IF I DO THAT TO YOU, IT'S NOTHING PERSONAL, BUT IN THE INTEREST OF FAIRNESS, MAKING SURE THAT EVERYONE WHO IS SCHEDULED TO SPEAK

GETS THEIR OPPORTUNITY, WE DON'T REALLY HAVE AN ALTERNATIVE. AND IN FACT, WE ARE HOPING THAT WE CAN FINISH THE AGENDA A LITTLE BIT EARLIER THAN WHAT'S LISTED, AND WE ARE PLANNING TO LIMIT LUNCH TO A HALF HOUR AS PART OF OUR EFFORTS TO FINISH A LITTLE BIT EARLY.
THE MOST IMPORTANT THING, I THINK, FOR EVERYONE ON THE PANEL AND IN THE AUDIENCE IS PLEASE MAKE SURE THAT YOU HAVE A COPY OF THE DISCUSSION QUESTIONS. IT'S THIS THING THAT SAYS JULY 2007 MEDCAC QUESTIONS, AND IT'S DATED JULY 17TH. THERE ARE COPIES OUTSIDE THE DOOR AND I THINK ALL THE PANEL MEMBERS SHOULD HAVE A COPY IN FRONT OF THEM, BECAUSE THIS IS GOING TO BE THE FOCAL POINT FOR ALL OF OUR DISCUSSIONS TODAY.
AND SO WITHOUT FURTHER ADO, WE WILL LAUNCH INTO THE INTRODUCTIONS OF THE PANEL MEMBERS. AND WHY DON'T WE START FROM THE FAR END THERE. AND I FORGOT TO MENTION THAT PANELISTS SHOULD STATE WHAT CONFLICTS YOU HAVE, IF ANY.
DR. TEXTOR: I'M STEPHEN TEXTOR FROM MAYO CLINIC IN ROCHESTER, MINNESOTA, A NEPHROLOGIST, AND I HAVE NO CONFLICTS IN THIS AREA.
DR. EDWARDS: MATT EDWARDS, A VASCULAR SURGEON FROM WAKE FOREST UNIVERSITY, AND I HAVE NO

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CONFLICTS.
DR. BERGTHOLD: LINDA BERGTHOLD, I'M THE CONSUMER REPRESENTATIVE. I'M AN INDEPENDENT HEALTHCARE CONSULTANT ON TECHNOLOGY ASSESSMENT ISSUES AND I HAVE NO CONFLICTS OF INTEREST.
MR. LACEY: MICHAEL LACEY. I'M THE DIRECTOR OF REIMBURSEMENT IN HEALTH ECONOMICS AT ACUSPHERE IN BOSTON AND I HAVE NO CONFLICTS.
DR. SLAUGHTER: MARK SLAUGHTER, A CARDIOTHORACIC SURGEON AT CHRIST HOSPITAL IN CHICAGO, AND I HAVE NO CONFLICTS.
DR. PRESSMAN: BARRY PRESSMAN FROM THE CEDARS SINAI MEDICAL CENTER, LOS ANGELES, A RADIOLOGIST. NO CONFLICTS.
DR. MAISEL: BILL MAISEL, A CARDIOLOGIST AT BETH ISRAEL DEACONESS MEDICAL CENTER AT HARVARD MEDICAL SCHOOL IN BOSTON, AND I HAVE NO CONFLICTS.
DR. LEWIS: I'M BILL LEWIS, I'M A CARDIOLOGIST IN CLEVELAND, OHIO AT CASE WESTERN RESERVE. I HAVE NO CONFLICTS.
DR. FENDRICK: MARK FENDRICK, GENERAL INTERNIST, HEALTH SERVICES RESEARCH, UNIVERSITY OF MICHIGAN. NO CONFLICTS.
DR. FLAMM: CAROLE FLAMM, ASSISTANT MEDICAL DIRECTOR FOR THE BLUE CROSS BLUE SHIELD

ASSOCIATION, AND I HAVE NO FINANCIAL CONFLICTS.
DR. CHARYTAN: I AM CHAIM CHARYTAN, CHIEF OF RENAL DIVISION AT NEW YORK HOSPITAL IN NEW YORK, QUEENS, AND ALSO WITH A LOT OF EXPERIENCE IN THE REGULATORY ISSUES. I WAS RECENTLY ASKED TO CHAIR A SAFETY MONITORING BOARD FOR A DEVICE FOR RENAL ARTERY STENTING, THAT'S A RECENT ISSUE THAT HAS COME UP. I AM NOT INVOLVED EXCEPT ON THE SAFETY MONITORING BOARD.
DR. KRIST: ALEX KRIST, A FAMILY PHYSICIAN AT VIRGINIA COMMONWEALTH UNIVERSITY, NO CONFLICTS.
DR. SALIVE: MARCEL SALIVE, MEDICAL OFFICER IN THE COVERAGE AND ANALYSIS GROUP.
DR. GARBER: AND AGAIN, I'M ALAN GARBER, WITH THE DEPARTMENT OF VETERANS AFFAIRS AND STANFORD UNIVERSITY, NO CONFLICTS.
AND I JUST WANT TO REMIND THE SPEAKERS, I BELIEVE WE'VE BEEN TOLD THIS BEFORE, BUT WHEN YOU SPEAK, PLEASE IDENTIFY YOURSELF, YOUR INSTITUTION AND ANY CONFLICTS YOU MIGHT HAVE, AND THIS IS FOR BOTH SCHEDULED SPEAKERS AND ANY PEOPLE WHO WANT TO SPEAK DURING THE OPEN AND PUBLIC COMMENTARY PERIOD. OKAY.
SO, WE WILL NOW HAVE THE PRESENTATION OF THE VOTING QUESTIONS BY SARAH MCCLAIN, FROM CMS.
MS. MCCLAIN: GOOD MORNING. WE'LL START

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OFF WITH INITIAL DISCUSSION QUESTION NUMBER 1.
CONSIDERING THE COMMON INCIDENTAL NATURE
OF ATHEROSCLEROTIC RENAL ARTERY STENOSIS, DISCUSS
THE:
DEGREE OF CORRELATION BETWEEN PERCENT
RENAL ARTERY STENOSIS AND KIDNEY FUNCTION.
ROLE OF TREATMENT CHOICE BASED UPON
PATIENT'S EXISTING MEDICAL CONDITION AND
COMORBIDITIES, LIKE RENOVASCULAR HYPERTENSION WITH OR
WITHOUT DIABETES, CHRONIC KIDNEY DISEASE,
HYPERLIPIDEMIA, PERIPHERAL VASCULAR DISEASE, CORONARY
ARTERY DISEASE, OR LEFT VENTRICULAR ABNORMALITIES.
INITIAL DISCUSSION QUESTION NUMBER 2.
DISCUSS THE ABILITY TO COMPARE STUDIES,
PERFORM META-ANALYSES AND DRAW VALID EVIDENCE-BASED
CONCLUSIONS BASED UPON EXISTING PUBLISHED
DEFINITIONS, MEASUREMENT TECHNIQUES, AND CRITERIA FOR
REPORTING PATIENT SELECTION, METHODS AND OUTCOMES.
SPECIFIC ISSUES FOR DISCUSSION ARE LISTED
ON PAGE THREE OF THE PACKET.
INITIAL DISCUSSION QUESTION NUMBER 3.
FOR BOTH STATE-OF-THE-ART PERCUTANEOUS
TRANSLUMINAL RENAL ANGIOPLASTY WITH STENTING
UTILIZING EMBOLIC PROTECTION AND SURGICAL RENAL
ARTERY RECONSTRUCTION, DISCUSS: DIAGNOSTIC TESTS OR

BASELINE PATIENT CHARACTERISTICS THAT ACCURATELY PREDICT POST-TREATMENT RENAL FUNCTION OUTCOMES; SUBGROUPS OF MEDICARE PATIENTS WITH ATHEROSCLEROTIC RENAL ARTERY STENOSIS WHO CLEARLY AND CONSISTENTLY BENEFIT FROM RENAL ANGIOPLASTY AND STENTING WITH EMBOLIC PROTECTION OR SURGICAL RENAL ARTERY RECONSTRUCTION; RISKS OF COMPLICATIONS FOR PATIENTS, ESPECIALLY THE OLDER MEDICATION POPULATION, WITH PROGRESSIVE RENAL DYSFUNCTION AND MULTIPLE COMORBIDITIES, ESPECIALLY POST-TREATMENT WORSENING RENAL FUNCTION AND HASTENING OF DIALYSIS.
VOTING QUESTION NUMBER 1.
FOR THE TREATMENT OF PATIENTS WITH ATHEROSCLEROTIC RENAL ARTERY STENOSIS, HOW CONFIDENT ARE YOU THAT THE EVIDENCE IS ADEQUATE TO DRAW CONCLUSIONS ABOUT SAFETY AND CLINICAL EFFECTIVENESS FOR THE FOLLOWING RENAL ARTERY INTERVENTIONS:
SURGICAL RENAL ARTERY RECONSTRUCTION;
RENAL ANGIOPLASTY WITHOUT STENT PLACEMENT;
RENAL ANGIOPLASTY AND STENTING WITH BARE METAL STENTS;
RENAL ANGIOPLASTY AND STENTING WITH DRUG-ELUTING STENTS.
ONE, NOT CONFIDENT, TO FIVE, HIGHLY CONFIDENT.

VOTING QUESTION NUMBER 2.
BASED ON THE EVIDENCE PRESENTED, HOW CONFIDENT ARE YOU THAT THE PUBLISHED RESULTS APPLY TO:

MEDICARE PATIENTS WITH TYPICAL COMORBIDITIES;

PROVIDERS, FACILITIES AND PHYSICIANS IN COMMUNITY PRACTICE; AND

PATIENT SUBGROUPS NOT REPRESENTED IN THE STUDY POPULATION.

ONE, NOT CONFIDENT, THROUGH FIVE, HIGHLY CONFIDENT.
VOTING QUESTION NUMBER 3.
BASED ON THE EVIDENCE PRESENTED FOR PATIENTS WITH ATHEROSCLEROTIC RENAL ARTERY STENOSIS, HOW CONFIDENT ARE YOU THAT COMPARED TO AGGRESSIVE MEDICAL TREATMENT ALONE, THERE ARE IMPROVED KEY HEALTH OUTCOMES ATTRIBUTABLE TO THE FOLLOWING CO-INTERVENTIONS:

SURGICAL RENAL ARTERY RECONSTRUCTION;

RENAL ANGIOPLASTY WITHOUT STENT PLACEMENT;

RENAL ANGIOPLASTY AND STENTING WITH BARE METAL STENTS;

RENAL ANGIOPLASTY AND STENTING WITH DRUG-ELUTING STENTS.

ONE, NOT CONFIDENT, THROUGH FIVE, HIGHLY CONFIDENT.

VOTING QUESTION NUMBER 4.

BASED ON THE EVIDENCE PRESENTED, SHOULD MEDICARE NATIONAL COVERAGE OF ANY NON-MEDICAL TREATMENTS FOR ATHEROSCLEROTIC RENAL ARTERY STENOSIS BE LIMITED ONLY TO PATIENTS ENROLLED IN QUALIFIED RESEARCH STUDIES?

ONE, STRONGLY AGREE, THROUGH FIVE, STRONGLY DISAGREE.

FINAL DISCUSSION QUESTION NUMBER 1.

DISCUSS STRENGTHS AND WEAKNESSES OF THE FOLLOWING ONGOING INTERNATIONAL TRIALS, ANY PROTOCOL CHANGES, AND IN YOUR OPINION THE ANTICIPATED VALIDITY OF THE DATA AND APPLICABILITY OF KEY HEALTH OUTCOMES TO MEDICARE PATIENTS WITH TYPICAL COMORBIDITIES IN COMMUNITY SETTINGS FOR STAR, RAVE, ASTRAL, NITER AND CORAL.

FINAL DISCUSSION QUESTION NUMBER 2.

DISCUSS PRACTICAL ISSUES AND MEDICAL/INTERVENTIONAL ENHANCEMENTS FOR FUTURE RANDOMIZED CONTROLLED TRIALS THAT MAY BE PLANNED OR ARE NEARLY READY TO BEGIN. SPECIFIC ISSUES FOR DISCUSSION ARE LISTED ON PAGE SIX OF THE PACKET.

DR. GARBER: NEXT WE WILL PROCEED TO THE

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PRESENTATION OF THE TECHNOLOGY ASSESSMENT BY ETHAN BALK FROM THE INSTITUTE FOR CLINICAL RESEARCH AND HEALTH POLICY STUDIES.

DR. BALK: MY NAME IS ETHAN BALK. I'M AT THE TUFTS NEW ENGLAND MEDICAL CENTER AT THE EVIDENCE-BASED PRACTICE CENTER. WE CONDUCTED A COMPARATIVE EFFECTIVENESS REPORT REVIEW OF MANAGEMENT STRATEGIES FOR RENAL ARTERY STENOSIS AND RECENTLY CONDUCTED AN UPDATE OF THAT REPORT FOR THIS MEETING.

JUST TO START WITH A LITTLE BACKGROUND, ATHEROSCLEROTIC RENAL ARTERY STENOSIS CAN RESULT IN REFRACTORY HYPERTENSION, CHRONIC KIDNEY DISEASE, MORBIDITIES ASSOCIATED WITH THESE CONDITIONS, AND THUS INCREASED MORTALITY. RENAL ARTERY STENOSIS OCCURS IN ABOUT 30 PERCENT OF PATIENTS WITH CARDIAC DISEASE AND UP TO 50 PERCENT OF THOSE HAVE DIFFUSE ATHEROSCLEROTIC VASCULAR DISEASES.

THE GOALS OF THERAPY GENERALLY ARE IMPROVEMENT IN THE UNCONTROLLED HYPERTENSION, PRESERVATION OR SALVAGE OF THE KIDNEY FUNCTION, IMPROVEMENT IN SYMPTOMS RELATED TO THE HYPERTENSION AND KIDNEY FUNCTION, AND ALSO IMPROVEMENT IN THE QUALITY OF LIFE.

AGGRESSIVE MEDICAL THERAPY IS WHAT IS AT LEAST AMONG MANY CIRCLES CONSIDERED TO BE THE

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APPROPRIATE MEDICAL APPROACH. IT CONSISTS OF A COMBINATION OF ANTIHYPERTENSIVE MEDICATION; LIPID-LOWERING AGENTS, PRIMARILY STATINS; AND ANTIPLATELET AGENTS, TO DECREASE THE RISK ASSOCIATED WITH ATHEROSCLEROTIC RENAL ARTERY STENOSIS. PATIENTS TREATED WITH MEDICAL THERAPY ALONE, HOWEVER, MAY BE AT RISK FOR DETERIORATION OF KIDNEY DISEASE, WORSENING MORBIDITY AND MORTALITY BECAUSE THE ATHEROSCLEROTIC PROCESS IS CONTINUING.

AN ALTERNATIVE IS REVASCULARIZATION. WHAT IS MOST COMMONLY USED CURRENTLY FOR THIS IS ANGIOPLASTY WITH STENT PLACEMENT. THE REVASCULARIZATION AT LEAST IN THEORY CAN HALT OR REVERSE THE PROGRESSION OF THE RENAL ARTERY STENOSIS BUT CARRIES SUBSTANTIAL RISKS OF MORBIDITY, MORTALITY, AND IT'S NOT CLEAR THAT IT AFFECTS THE UNDERLYING KIDNEY DISEASE.

SO AGAIN, THE CURRENT MEDICAL THERAPY GENERALLY CONSISTS OF COMBINATIONS OF BLOOD PRESSURE MEDICATIONS, AGAIN CURRENTLY MOSTLY ACE INHIBITORS, ANGIOTENSIN RECEPTOR BLOCKERS, AND ALSO CALCIUM CHANNEL BLOCKERS AND BETA BLOCKERS. STATINS AND ANTIPLATELET AGENTS ARE ALSO USED.

AS I MENTIONED, ANGIOPLASTY WITH STENT PLACEMENT IS THE MOST COMMONLY USED REVASCULARIZATION

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PROCEDURE NOW. ANGIOPLASTY ALONE IS RELATIVELY INFREQUENT. HOWEVER, IT'S NOTABLE THAT AT LEAST TO THE BEST OF OUR KNOWLEDGE, THERE IS NO MARKETED STENT THAT IS CURRENTLY FDA-APPROVED FOR RENAL ARTERY STENOSIS. THERE ARE FDA-APPROVED STENTS BUT THEY'RE NOT MARKETED. OPEN SURGICAL BYPASS IS GENERALLY RESERVED FOR PATIENTS WITH COMPLICATED DISEASE, PARTICULARLY THOSE WITH CONCURRENT AORTIC DISEASE OR ANEURYSMS OR OTHER MIXED DISEASES.

THERE ARE NO PUBLISHED TRIALS THAT DIRECTLY COMPARE THESE TWO APPROACHES, AGGRESSIVE MEDICAL THERAPY AND ANGIOPLASTY WITH STENT. THERE ARE SOME ONGOING PUBLISHED TRIALS, AS WAS NOTED IN THE DISCUSSION QUESTIONS.

SO, WE WERE ASKED TO FIND THE EVIDENCE TO ANSWER THREE PRIMARY QUESTIONS. THE FIRST ONE WAS, FOR PATIENTS WITH ATHEROSCLEROTIC RENAL ARTERY STENOSIS, WHAT IS THE EVIDENCE ON THE EFFECTS OF AGGRESSIVE MEDICAL THERAPY VERSUS ANGIOPLASTY WITH STENT PLACEMENT ON LONG-TERM CLINICAL OUTCOMES? AND WE DEFINED THAT WITH A GROUP OF DOMAIN EXPERTS AS BEING AT LEAST SIX MONTHS. WE ALSO LOOKED AT ADVERSE EVENTS.

THE SECOND AND THIRD QUESTIONS ARE BRIEFLY, WHAT CLINICAL, IMAGING, LABORATORY AND

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ANATOMIC CHARACTERISTICS ARE ASSOCIATED WITH IMPROVED OR WORSE OUTCOMES AFTER TREATMENT WITH THE VARIOUS INTERVENTIONS, AND WHAT ADJUNCT INTERVENTIONS ARE ASSOCIATED WITH IMPROVED OR WORSE OUTCOMES AFTER RENAL ARTERY ANGIOPLASTY WITH STENT PLACEMENT?

SO WE PERFORMED A SEARCH OF THE LITERATURE, PRIMARILY IN MEDLINE. WE UPDATED THE SEARCH IN APRIL OF 2007 AND LOOKED ONLY AT ENGLISH LANGUAGE ARTICLES. THE POPULATION OF INTEREST WAS ADULTS WITH ATHEROSCLEROTIC RENAL ARTERY STENOSIS. WE EXCLUDED STUDIES OF RENAL ARTERY STENOSIS IN THE SETTING OF KIDNEY TRANSPLANTS, RENAL ARTERY ANEURYSMS REQUIRING REPAIR, AORTIC DISEASE REQUIRING REPAIR, STUDIES WHERE MORE THAN 20 PERCENT OF THE PATIENTS HAD A PREVIOUS REVASCULARIZATION PROCEDURE, AND STUDIES WHERE MORE THAN 20 PERCENT OF THE PATIENTS HAD OTHER CAUSES OR RENAL ARTERY STENOSIS, PRIMARILY FIBROMUSCULAR DYSPLASIA.

THE INTERVENTIONS OF INTEREST. AS I NOTED, THE PRIMARY ONES WERE A COMBINATION OF MEDICAL TREATMENTS, ANTIHYPERTENSIVE, ANTIHYPERLIPIDEMIA, ANTIPLATELET DRUGS, COMPARED TO ANGIOPLASTY WITH STENT PLACEMENT.

KNOWING THAT THE EVIDENCE ON THIS WAS GOING TO BE SOMEWHAT LIMITED, WE BROUGHT IN THE

INTERVENTION OF INTEREST TO ANY MEDICAL TREATMENT USED FOR RENAL ARTERY STENOSIS, ANGIOPLASTY WITHOUT STENT PLACEMENT AND ALSO OPEN SURGICAL REVASCULARIZATION. WE ALSO LOOKED AT NATURAL HISTORY STUDIES, MEANING STUDIES WHERE THEY JUST FOLLOWED PATIENTS WITH THE DISEASE WITHOUT A SPECIFIC PROTOCOL, OR STUDIES WHERE THEY DIDN'T DESCRIBE AT ALL WHAT MEDICATIONS WERE BEING USED. HOWEVER, I'M NOT GOING TO DISCUSS THOSE STUDIES HERE.

THE OUTCOMES OF INTEREST WERE PRIMARILY LONG-TERM CLINICAL OUTCOMES, DEFINED AS AT LEAST SIX MONTHS AFTER THE INTERVENTION WAS STARTED OR THE ANGIOPLASTY WAS PERFORMED, AND ADVERSE EVENTS. SPECIFICALLY THESE INCLUDED MORTALITY, KIDNEY FUNCTION, BLOOD PRESSURE CONTROL, CARDIOVASCULAR EVENTS WHICH I'M NOT GOING TO DESCRIBE IN MUCH DETAIL BECAUSE THE EVIDENCE WAS FAIRLY SPOTTY, QUALITY OF LIFE, RESTENOSIS AFTER ANGIOPLASTY WITH STENT PLACEMENT, WHICH AGAIN, I'M NOT GOING TO PRESENT HERE, AND ADVERSE EVENTS.

WE USED DIFFERENT ELIGIBILITY CRITERIA FOR DIFFERENT TYPES OF STUDIES BASED ON THE LIKELY IMPACT OF THOSE STUDIES ON OUR CONCLUSIONS, AND ALSO BASED ON THE QUANTITY OF EVIDENCE THAT WE EXPECTED TO FIND. SO FOR COMPARATIVE STUDIES, THOSE THAT COMPARE

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MEDICAL THERAPY TO REVASCULARIZATION, THOSE WERE OF PRIMARY INTEREST SO WE INCLUDED ANY OF THOSE STUDIES, PROSPECTIVE, RETROSPECTIVE, RANDOMIZED, NONRANDOMIZED, THEY HAD TO HAVE AT LEAST TEN PATIENTS, AND THEY COULD HAVE BEEN DONE AT ANY TIME IN THE PAST. THE REST OF THE STUDIES WERE COHORT STUDIES, PRE-POST STUDIES WHERE IT LOOKED AT ONLY A SINGLE GROUP OF PATIENTS RECEIVING A SINGLE INTERVENTION WITHOUT A DIRECT COMPARISON. FOR MEDICINE, COHORTS OF MEDICINE INTERVENTION, WE INCLUDED PROSPECTIVE STUDIES WITH AT LEAST TEN PATIENTS.

FOR ANGIOPLASTY AND STENT COHORTS, WE QUICKLY FOUND THAT THERE WERE A REASONABLE NUMBER OF THESE STUDIES, SO WE LIMITED THESE TO PROSPECTIVE STUDIES WITH AT LEAST 30 PEOPLE. WE ALSO LIMITED THESE AND OTHER SURGICAL STUDIES TO THOSE STUDIES PERFORMED AFTER 1993. THIS DATE WAS CHOSEN BECAUSE THAT WAS ABOUT WHEN JNC-5 CAME OUT, WHICH ADVOCATED A STRICTER CONTROL OF BLOOD PRESSURE. IT WAS ALSO ABOUT THE SAME TIME THAT ACE INHIBITORS STARTED TO BE COMMONLY USED. SO IT'S A TIME FRAME THAT'S MOST RELEVANT TO CURRENT PRACTICE.

AND THEN THE SURGICAL COHORTS. WE INCLUDED ANY PROSPECTIVE STUDIES THAT WERE DONE

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RECENTLY. FOR THE RETROSPECTIVE STUDIES, BECAUSE THERE WERE A LARGE NUMBER OF SMALL STUDIES THAT WERE HARD TO INTERPRET, WE LIMITED THOSE TO THE LARGER RETROSPECTIVE STUDIES.

FOR THE PURPOSE OF UNDERSTANDING THE EVIDENCE, WE CREATED THESE TIERS OF EVIDENCE, WHICH WERE USED TO HELP US DESCRIBE THE RELEVANCE OF THE STUDIES TO THE PRIMARY QUESTIONS OF INTEREST. SO THE TIER I STUDIES WOULD BE RANDOMIZED CONTROLLED TRIALS THAT SPECIFICALLY COMPARE STENT TO AGGRESSIVE MEDICAL THERAPY. TIER II STUDIES WERE OTHER RANDOMIZED TRIALS THAT COMPARED ANGIOPLASTY WITH OR WITHOUT STENT TO ANY MEDICAL INTERVENTION THAT HAD AT LEAST A SIX-MONTH FOLLOW-UP SINCE THOSE WERE OUR OUTCOMES OF INTEREST, FOR SIX MONTHS.

THE TIER III EVIDENCE FOR OTHER COMPARATIVE STUDIES HAD TO BE A DIRECT COMPARISON, BUT COULD BE ANY INVASIVE INTERVENTION, INCLUDING SURGERY, VERSUS MEDICAL, AND WE DIDN'T HAVE THE TIME RESTRICTION OR FOLLOW-UP RESTRICTION. AND THEN TIER IV EVIDENCE WERE THE COHORT STUDIES, AGAIN, THAT DID NOT MAKE A DIRECT COMPARISON.

WE GRADED THESE STUDIES FOR METHODOLOGICAL QUALITY. THIS IS SOMETHING THAT WE COMMONLY DO AND WE HAVE MANY YEARS OF EXPERIENCE DOING. WE FIND THAT

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IT IS VERY USEFUL TO UNDERSTANDING WHAT THE OVERALL EVIDENCE FINDS AND WE FIND THAT ALSO, WE'RE ABLE TO CONSISTENTLY GRADE STUDIES ACROSS DIFFERENT TOPICS AND DOMAINS. SO WE USED THE THREE-TIER SCALE, GOOD, FAIR AND POOR.

GOOD QUALITY STUDIES ARE THOSE THAT ADHERE TO COMMONLY HELD CONCEPTS OF HIGH QUALITY. IN THIS CASE THEY HAD TO BE RANDOMIZED TRIALS THAT WERE WELL DESCRIBED, GOOD REPORTING, NO OBVIOUS ERRORS, APPROPRIATE METHODOLOGY WAS USED, AND A SMALL WITHDRAWAL RATE. FAIR QUALITY STUDIES WERE POSSIBLY SUSCEPTIBLE TO SOME BIAS BUT THE PROBLEMS WERE NOT SUFFICIENT TO INVALIDATE THE RESULTS. THERE WERE SOME DEFICIENCIES IN THESE STUDIES. POOR QUALITY STUDIES, THERE WERE SUBSTANTIAL PROBLEMS THAT MADE US THINK THERE WAS SIGNIFICANT BIAS OR SIGNIFICANT BIAS COULDN'T BE RULED OUT; THESE INCLUDED SERIOUS METHODOLOGICAL ERRORS, LARGE AMOUNTS OF MISSING INFORMATION AND DISCREPANCIES IN REPORTING.

SIMILARLY, WE ALSO WEIGHTED THE APPLICABILITY OF THE STUDIES. THIS RELATED PRIMARILY TO THE STUDY POPULATION AND ONLY INDIRECTLY TO THE RELEVANCE OF THE OVERALL TOPIC OF THE OVERALL STUDY TO CURRENT MEDICAL PRACTICE, WHICH WAS CAPTURED IN THE TIERS OF EVIDENCE. SO WE RATED THE STUDIES AS

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HIGH APPLICABILITY, MODERATE APPLICABILITY, AND LOW APPLICABILITY.
BRIEFLY, HIGH APPLICABLE STUDIES ARE THOSE THAT ARE REPRESENTATIVE OF TARGET POPULATION, IN THIS CASE THEY HAD A RANGE OF STENOSIS THAT VARIED AND THE AVERAGE PATIENT WAS BROADLY SIMILAR TO THE TYPICAL PATIENT WHO IS RECEIVING THERAPY FOR RENAL ARTERY STENOSIS, AND THESE HAD TO HAVE AT LEAST 30 PATIENTS. MODERATE APPLICABLE STUDIES INCLUDED A RELEVANT SUBGROUP. LOW APPLICABLE STUDIES HAD A NARROW SUBGROUP WITH LIMITED APPLICABILITY OR THEY WERE FAIRLY OLD STUDIES, BEFORE JNC-5.
WE ALSO EVALUATED THE STRENGTH OF THE EVIDENCE TO HELP US DRAW CONCLUSIONS ABOUT THE EVIDENCE. WE GRADED THE EVIDENCE AS EITHER -- ONE THING TO NOTE ABOUT THIS IS THAT ALL OF THESE RATING SYSTEMS ARE SOMEWHAT SUBJECTIVE, BUT THERE'S PROBABLY MORE SUBJECTIVITY TO THIS. WE DID USE OUR OWN BEST UNDERSTANDING OF IT AND ALSO CONSULTED WITH VARIOUS DOMAINS AND OTHER METHODOLOGICAL EXPERTS, GOT A FAIR AMOUNT OF INPUT TO HELP US COME TO THESE CONCLUSIONS.
SO ROBUST EVIDENCE WOULD BE WHEN THERE'S A HIGH LEVEL OF ASSURANCE IN THE VALIDITY OF THE RESULTS BASED ON THE QUALITY OF THE STUDIES, THE APPLICABILITY, THE EFFECT SIZE AND THE CONSISTENCY.

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THERE WOULD HAVE HAD TO HAVE BEEN AT LEAST TWO HIGH QUALITY STUDIES WITH LONG-TERM FOLLOW-UP AND NO IMPORTANT DISAGREEMENT ACROSS THE STUDIES.
ACCEPTABLE STUDIES, ACCEPTABLE STRENGTH OF EVIDENCE WAS WHEN THERE WAS GOOD TO MODERATE LEVEL OF ASSURANCE IN THE VALIDITY OF THE RESULTS, LITTLE DISAGREEMENT.
WEAK EVIDENCE, THERE WAS LOW LEVEL OF ASSURANCE OF THE VALIDITY OF THE RESULTS. THESE WERE BASED ON STUDIES OF MODERATE TO POOR QUALITY, LIMITED APPLICABILITY.
AND THEN THERE WAS A CATEGORY OF INCONSISTENT EVIDENCE, WHEN THERE WAS DISAGREEMENT EITHER WITHIN OR ACROSS STUDIES.
SO AS FAR AS HOW WE SYNTHESIZED THE DATA, WE WENT INTO THIS THINKING THAT WE MIGHT BE ABLE TO DO META-ANALYTIC TECHNIQUES, MATHEMATICAL TECHNIQUES TO DEFINE THE DATA, BUT WE QUICKLY FOUND THAT THE RANDOMIZED TRIAL DATA WAS TOO SPARSE TO DO THIS IN A MEANINGFUL WAY. THE COHORT STUDIES TENDED TO BE TOO HETEROGENEOUS IN TERMS OF THE POPULATION, SPECIFIC INTERVENTIONS, THE FOLLOW-UP TIMES, THE OUTCOME DEFINITIONS. SO GIVEN THE STATE OF THE EVIDENCE, WE CONCLUDED THAT A META-ANALYSIS WOULD NOT HAVE IMPROVED MEANINGFUL COMPARISONS ACROSS THE

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INTERVENTIONS.
SO, THESE ARE THE AVAILABLE STUDIES. WE SCREENED THROUGH A BIT MORE THAN 2,300 CITATIONS IN MEDLINE AND FOUND 68 UNIQUE STUDIES. AS I SAID, WE GROUPED THESE BASED ON THE EVIDENCE TIER AND THAT'S HOW THIS TABLE WAS SET UP. MOST IMPORTANTLY, FOR TIER I EVIDENCE DIRECTLY COMPARING STENT TO TRIPLE THERAPY, AGGRESSIVE THERAPY, AS YOU KNOW, THERE ARE NO STUDIES.
FOR TIER II EVIDENCE, RANDOMIZED TRIALS OF ANGIOPLASTY VERSUS ANY MEDICAL THERAPY WITH AT LEAST SIX-MONTH FOLLOW-UP, THERE WERE ONLY TWO TRIALS, WITH ONLY A HUNDRED PATIENTS.
AND FOR THE TIER III EVIDENCE WE HAD NINE STUDIES, AND THEN FOR THE TIER IV STUDIES OF THE DIFFERENT INTERVENTIONS, THE COHORT STUDIES, WE NOTE THERE WERE VERY FEW STUDIES OF MEDICAL TREATMENTS, SURGERY, AND THERE WERE 28 STENT STUDIES THAT WE LOOKED AT. SO OVERALL THE QUALITY WAS FAIR TO POOR, ABOUT HALF AND HALF, AND MOST OF THE STUDIES WERE OF MODERATE TO LOW APPLICABILITY.
SO LET ME START WITH THE TIER II TRIALS.
THERE WERE TWO OF THESE, THE SCOTTISH-NEWCASTLE TRIAL WRITTEN UP BY WEBSTER AND COLLEAGUES, AND THE EMMA TRIAL BY PLOUIN AND COLLEAGUES, BOTH PUBLISHED IN

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1998. THEY BOTH INCLUDED PATIENTS WITH RESISTANT HYPERTENSION. THE EMMA TRIAL USED A SLIGHTLY HIGHER THRESHOLD FOR RENAL ARTERY STENOSIS, SLIGHTLY MORE SEVERE DISEASE. HOWEVER, THEY RESTRICTED THE POPULATIONS TO THOSE WITHOUT SEVERE CHRONIC KIDNEY DISEASE. THE EMMA STUDY RESTRICTED THE POPULATION TO THOSE WITH UNILATERAL DISEASE AND THE WEBSTER TRIAL INCLUDED ABOUT HALF THE PATIENTS, HALF THE PATIENTS WITH BILATERAL DISEASE AND HALF WITH UNILATERAL DISEASE.

BOTH OF THE TRIALS WERE SMALL, EACH HAD ABOUT 25 PATIENTS WHO RECEIVED ANGIOPLASTY AND ABOUT 25 OR 30 PATIENTS WHO RECEIVED MEDICAL THERAPY. NOTABLY IN THE WEBSTER TRIAL, FIVE OF THE 25 PATIENTS AFTER SIX MONTHS WENT ON TO HAVE EITHER NEPHRECTOMY OR OTHER SURGICAL BYPASS, AND FIVE OF THE PATIENTS WHO WERE ASSIGNED TO MEDICAL THERAPY AFTER SIX MONTHS SUBSEQUENTLY HAD ANGIOPLASTY. IT'S ALSO NOTABLE THAT ALMOST NONE OF THE PATIENTS RECEIVED STENTS.

FOR THE MEDICATIONS, THE WEBSTER TRIAL --

BOTH STUDIES USED A VARIETY OF MEDICATIONS. THE WEBSTER TRIAL DID NOT USE ANY ACE INHIBITORS AND ONLY SOME OF THE PATIENTS IN THE EMMA TRIAL USED ENALAPRIL.

BOTH HAD A PRIMARY ENDPOINT AT SIX MONTHS.

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THE WEBSTER STUDY ALSO FOLLOWED PATIENTS FOR UP TO 54 MONTHS AFTER THE RANDOMIZATION PERIOD WAS OVER AND AGAIN AFTER THERE WAS SOME CROSSOVER.
BOTH OF THE STUDIES WERE RATED TO BE FAIR QUALITY AND ONE WAS OF MODERATE APPLICABILITY, ONE LOW APPLICABILITY, PRIMARILY BECAUSE THEY EXCLUDED PATIENTS WITH BILATERAL DISEASE.
SO TO REITERATE, THESE STUDIES HAD LIMITED RELEVANCE TO CURRENT PRACTICE BECAUSE VERY FEW OF THE PATIENTS WERE ON ACE INHIBITORS. STATINS AND ANTIPLATELET DRUGS WERE NOT IN THE PROTOCOLS.
ESSENTIALLY NONE OF THE PATIENTS WHO HAD ANGIOPLASTY ALSO HAD STENT. THE SAMPLE SIZES WERE VERY SMALL, ONLY ABOUT 50 PATIENTS EACH. THESE WERE NOT POWERED FOR ANY CLINICAL EVENT, AS I WILL POINT OUT LATER AGAIN, AND A SUBSTANTIAL NUMBER CROSSED OVER TO EITHER ANGIOPLASTY OR BYPASS. AND IT WAS, EVEN THOUGH IT MET OUR CRITERIA, THERE WAS NO SHORT-TERM FOLLOW-UP, ONLY A SIX-MONTH FOLLOW-UP FOR THE PRIMARY OUTCOME.
THE TIER III STUDIES, THE OTHER COMPARATIVE STUDIES, NONE OF THEM USED STENTS AND NONE OF THEM HAD AGGRESSIVE MEDICAL THERAPY, MEANING TRIPLE THERAPY. THE DRASTIC STUDY, WHICH IS ANOTHER RANDOMIZED TRIAL WHICH IS OFTEN LUMPED, OR IT'S NOT

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LUMPED, BUT IT'S OFTEN GROUPED WITH THE OTHER TWO TRIALS, AND IF YOU'RE FAMILIAR WITH THE COCHRANE REVIEW ON THIS TOPIC, THEY INCLUDED ALL THREE TRIALS. SO THE DRASTIC STUDY WAS A TRIAL OF ANGIOPLASTY VERSUS AMLODIPINE OR ENALAPRIL, BUT IMPORTANTLY AT THREE MONTHS, HALF OF THE PEOPLE IN THE DRUG ARM RECEIVED ANGIOPLASTY. THERE WERE EIGHT OTHER STUDIES OF VARIOUS TYPES. MOST OF THE STUDIES WERE OF POOR QUALITY, MOST OF THEM WERE CONSIDERED TO BE OF LOW APPLICABILITY.

FOR THE TIER IV STUDIES, THE COHORT STUDIES OF MEDICINE, THERE WERE FOUR PROSPECTIVE STUDIES, THESE WERE LIMITED TO PROSPECTIVE STUDIES, WITH ONLY 83 PATIENTS IN TOTAL. THESE WERE A VARIETY OF MEDICAL REGIMENS BUT AT LEAST MOSTLY INCLUDING ACE INHIBITORS. THESE WERE GENERALLY OF POOR QUALITY AND LOW APPLICABILITY. THERE WERE ALSO THREE OTHER STUDIES THAT ONLY PROVIDED DATA ON ADVERSE EVENTS.

WITH THE ANGIOPLASTY AND STENT COHORTS, WE FOUND 28 STUDIES. AGAIN, THESE WERE LIMITED TO PROSPECTIVE STUDIES WITH AT LEAST 30 PATIENTS WHO HAD THEIR INTERVENTIONS AFTER STARTING IN 1993. THERE WERE ALMOST 4,000 PATIENTS WITH A WIDE RANGE OF FOLLOW-UP TIMES AND HALF FAIR, HALF POOR QUALITY. AND MOSTLY, OR ABOUT HALF OF THE STUDIES HAD MODERATE

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APPLICABILITY, SOME WITH HIGH APPLICABILITY. AND THE SURGICAL BYPASS COHORTS, THERE WERE FOUR OF THEM THAT MET CRITERIA. THEY ALL WERE RETROSPECTIVE, AND AGAIN THESE HAD AT LEAST A HUNDRED PATIENTS, WHERE MOST OF THE PATIENTS HAD THE PROCEDURE DONE SINCE 1993. THERE WERE NO ELIGIBLE PROSPECTIVE STUDIES. THERE WERE ALMOST A THOUSAND PATIENTS WITH UP TO 17 YEARS FOLLOW-UP. ALL OF THESE WERE OF POOR QUALITY AND LOW APPLICABILITY.

SO MOVING ON TO THE RESULTS OF OUR FINDINGS, THE STUDIES OF MORTALITY, FOR THE TIER II STUDIES, ONLY THE WEBSTER STUDY REPORTED ON MORTALITY. THEY COMBINED THEIR DATA FROM UNILATERAL AND BILATERAL GROUPS, AND LOOKED OVER THE 42 MONTHS. THE SURVIVAL CURVES WERE NEARLY IDENTICAL BETWEEN THE TWO INTERVENTIONS. HOWEVER, IMPORTANTLY, WITH ONLY 50 PEOPLE TOTAL, IT WAS CLEARLY UNDERPOWERED TO DETECT ANY DIFFERENCES IN MORTALITY.

AMONG THE OTHER COMPARATIVE STUDIES, FOUR OF THE FIVE STUDIES FOUND NO DIFFERENCE IN MORTALITY. AGAIN, THEY WERE ALL SMALL AND UNDERPOWERED. THERE WAS ONE RETROSPECTIVE STUDY THAT DID FIND A DIFFERENCE WITH HIGHER MORTALITY IN THE MEDICAL TREATMENT ARM, BUT IT'S IMPORTANT TO NOTE THAT IT WAS A RETROSPECTIVE STUDY AND THERE WERE MANY PATIENTS IN

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THE MEDICAL ARM WHO DID NOT RECEIVE SURGERY BECAUSE THEIR COMORBIDITIES WERE SO SEVERE, THEY WERE CONSIDERED HIGH SURGICAL RISK.

AND THEN WITH THE INDIRECT COMPARISONS BETWEEN THE COHORT STUDIES, THERE WAS A WIDE ARRAY OF DATA AND WE BASED, SIMPLY OUR SUMMARY WAS THAT, OR OUR CONCLUSION WAS THAT WE COULDN'T FIND ANY DIFFERENCES IN MORTALITY ACROSS THE STUDIES IN THE INTERVENTIONS.

SO MOVING ON TO KIDNEY FUNCTION, AGAIN THIS IS GOING BACK TO THE TIER II STUDIES, THE RANDOMIZED TRIALS, BOTH OF THEM FOUND NO SIGNIFICANT DIFFERENCE IN KIDNEY FUNCTION. THE CHANGES IN KIDNEY FUNCTION WERE RELATIVELY SMALL, BUT WITHIN THIS DEGREE OF NONSIGNIFICANCE WERE INSIGNIFICANT, OR INCONSISTENT.

SO ON THE LEFT HERE IS THE WEBSTER STUDY THAT REPORTED CHANGE IN SERUM CREATININE. ON THE RIGHT IS THE PLOUIN, THE EMMA STUDY THAT REPORTED CHANGE IN CREATININE CLEARLY. WE ATTEMPTED TO PUT THIS ON ABOUT THE SAME SCALE, BUT IT'S DIFFICULT TO DO. SO THE BLUE AND THE GREEN ARE ANGIOPLASTY, THE RED AND THE PINK -- I'M SORRY. THE BLUE AND THE GREEN ARE MEDICATION, THE RED AND THE PINK ARE ANGIOPLASTY. SIX-MONTH DATA AND FINAL DATA UP TO 54

00035

MONTHS FOR WEBSTER. AND SO AGAIN, NONSIGNIFICANT, BUT WITHIN THAT, SOMETIMES MEDICATION PATIENTS GOT WORSE, HAD THEIR KIDNEY FUNCTION WORSEN MORE ON MEDICATION THAN WITH ANGIOPLASTY, BUT SOMETIMES THE CREATININE GOT WORSE ON ANGIOPLASTY. THE WEBSTER STUDY DID REPORT ON END-STAGE RENAL DISEASE DEVELOPMENT AND FOUND SIMILAR RATES OF EVENTS, ABOUT EIGHT AND SEVEN PERCENT, COMBINING BILATERAL AND UNILATERAL ARMS.

AMONG THE TIER III, THE OTHER COMPARATIVE STUDIES, THERE WERE INCONSISTENT FINDINGS ABOUT KIDNEY FUNCTION, OR THE STUDIES FOUND THAT ANGIOPLASTY WAS BETTER THAN MEDICAL THERAPY. ONE OF THE STUDIES FOUND THAT THE MEDICAL THERAPY WAS BETTER THAN ANGIOPLASTY OR SURGERY, AND THREE OF THE STUDIES FOUND NO DIFFERENCE IN KIDNEY FUNCTION. ONLY ONE OF THE EIGHT COMPARATIVE STUDIES FOUND THAT KIDNEY FUNCTION ON AVERAGE IMPROVED FROM BASELINE AFTER ANGIOPLASTY OR SURGERY, IN CONTRAST TO THE MEDICAL ARM.

AMONG THE TIER IV STUDIES FOR KIDNEY FUNCTION, TWO OF THE MEDICATION STUDIES, EITHER MULTIDRUG OR ENALAPRIL, FOUND THAT SERUM CREATININE ON AVERAGE ROSE .1 TO .3 MILLIGRAMS PER DECILITER, AND GFR DECREASED BY A SMALL AMOUNT, FOUR MILLIMETERS

PER MINUTE, ABOUT SIX PERCENT.
22 OF THE STENT COHORTS FOUND ON AVERAGE
THAT SERUM CREATININE DROPPED A SMALL AMOUNT, .1, BUT
THERE WAS A WIDE RANGE IN CHANGE IN SERUM CREATININE
FROM A DECREASE OF 1.1 TO AN INCREASE OF .2
MILLIGRAMS PER DECILITER ON AVERAGE. GFR ON AVERAGE
WENT UP BY A SMALL AMOUNT, WITH A FAIRLY NARROW RANGE
OF CHANGE. HOWEVER, THEY FOUND THAT WITHIN STUDIES,
EIGHT TO 51 PERCENT OF THE PATIENTS IMPROVED THEIR
KIDNEY FUNCTION.
THERE WERE THREE OF THE SURGICAL STUDIES
REPORTING ON KIDNEY FUNCTION. ONE FOUND THAT 74
PERCENT OF THE PATIENTS WERE FREE OF CHRONIC KIDNEY
DISEASE AT FIVE YEARS. ONE FOUND THAT GFR ON AVERAGE
ROSE BY SEVEN MILLILITERS PER MINUTE, BUT THAT 17
PERCENT OF THE PATIENTS DEVELOPED END-STAGE RENAL
DISEASE. AND A THIRD STUDY FOUND THAT 72 PERCENT OF
THE PATIENTS EITHER HAD IMPROVED OR UNCHANGED KIDNEY
FUNCTION, BUT AGAIN, 17 PERCENT DEVELOPED KIDNEY
FAILURE.
MOVING ON TO BLOOD PRESSURE, GOING BACK TO
THE TIER II RANDOMIZED TRIALS, AGAIN, FEW OF THESE
STUDIES LOOKED AT ACE INHIBITORS. THE FINDINGS WERE
INCONSISTENT. WEBSTER FOUND THAT -- SO I'VE GOT
SYSTOLIC PRESSURE HERE, DIASTOLIC PRESSURE HERE,

00037

UNILATERAL DISEASE TO THE LEFT, BILATERAL DISEASE ON THE RIGHT, AND WEBSTER IS HERE. SO WEBSTER IS HERE, EMMA IS HERE, THIS IS THE LONG-TERM FOLLOW-UP FOR WEBSTER AND FOR BILATERAL, BOTH OF THESE ARE WEBSTER AT SIX MONTHS AND FINAL.

SO AT SIX MONTHS FOR BOTH STUDIES, THERE WERE NO SIGNIFICANT CHANGES. AGAIN THESE ARE PRIMARY ENDPOINTS, WHETHER UNILATERAL OR BILATERAL DISEASE.

BUT, THERE WAS A FINDING THAT ANGIOPLASTY WAS SIGNIFICANTLY BETTER FOR BILATERAL DISEASE AT THE FINAL TIME BETWEEN THREE AND FOUR TO 54 MONTHS, BUT AGAIN, THERE WAS SOME CROSSOVER AT SIX MONTHS.

THE PLOUIN STUDY ALSO DID FIND A BENEFIT IN DIASTOLIC BLOOD PRESSURE BUT NOT SYSTOLIC BLOOD PRESSURE AFTER AN ANGIOPLASTY, AND THIS WAS IN THE UNILATERAL GROUP OF PATIENTS.

AMONG THE TIER III STUDIES, THE OTHER COMPARATIVE STUDIES, THERE WERE EIGHT STUDIES. MOST FOUND NO DIFFERENCE IN BLOOD PRESSURE BETWEEN THE DIFFERENT INTERVENTIONS. SIX OF THE STUDIES FOUND NO SIGNIFICANT DIFFERENCE. THERE WAS A MIX OF WHETHER THE INVASIVE OR THE DRUG THERAPIES WERE BETTER WITHIN THAT CONSTRAINT. TWO OF THE STUDIES DID FIND THAT ANGIOPLASTY RESULTED IN SIGNIFICANTLY BETTER BLOOD PRESSURE RESULTS THAN MEDICAL THERAPY.

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AMONG THE COHORT STUDIES, THE FOUR MEDICATION STUDIES, ALL FOUND THAT ON AVERAGE PATIENTS DID DO WELL, MEDICATION WAS EFFECTIVE AT LOWERING BLOOD PRESSURE.
AMONG THE STENT STUDIES, THERE WERE 27.
IN GENERAL, AGAIN, THEY FOUND THE DECREASE IN BLOOD PRESSURE. WITHIN STUDIES, 18 PERCENT OF PATIENTS HAD CURE OF HYPERTENSION, MEANING THAT THEY NO LONGER REQUIRED MEDICATION TO CONTROL THEIR BLOOD PRESSURE, AND WITHIN STUDIES, 35 TO 79 PERCENT OF PATIENTS HAD IMPROVEMENT IN THEIR BLOOD PRESSURE.
AMONG TWO SURGICAL STUDIES, ONE OF THE STUDIES FOUND A LARGE DECREASE IN BLOOD PRESSURE, 53 OVER 23 MILLIMETERS OF MERCURY, 68 PERCENT OF THE PATIENTS AT THREE YEARS AND 59 PERCENT OF THE PATIENTS AT FIVE YEARS HAD EITHER CURE OR IMPROVEMENT IN THEIR HYPERTENSION. AND IN THE OTHER STUDY, 12 PERCENT OF THE PATIENTS HAD CURE IN THE HYPERTENSION, AND AT EIGHT WEEKS, 73 PERCENT HAD SOME IMPROVEMENT IN THEIR HYPERTENSION.
ONE STUDY, THE DRASTIC STUDY RECENTLY REPORTED ON QUALITY OF LIFE. THEY LOOKED AT ONLY THE COMPARISON OF ANGIOPLASTY ALONE AND MEDICATION ALONE, SO THE PATIENTS WHO SWITCHED OVER AT THREE MONTHS WERE DROPPED FROM THIS EVALUATION. SO THEY FOUND

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THAT FOR PHYSICAL SYMPTOMS ASSOCIATED WITH HYPERTENSION, THERE WAS A DECREASED NUMBER OF COMPLAINTS, A LARGER DECREASE IN THE NUMBER OF COMPLAINTS AFTER ANGIOPLASTY, BUT THIS WAS NOT A SIGNIFICANT FINDING.

THE OVERALL SF-36 AND EUROQOL WAS NO DIFFERENT AFTER THE TWO INTERVENTIONS, BUT FOR THE SOCIAL FUNCTIONING PORTION OF SF-36, THEY FOUND INCONSISTENT RESULTS AT THREE VERSUS 12 MONTHS. BASICALLY THERE WAS A FLIP IN WHICH WAS -- BOTH AT THREE AND 12 MONTHS THERE WAS STATISTICALLY SIGNIFICANT FINDINGS, BUT THERE WAS A SWITCH AS FAR AS WHICH INTERVENTION WAS BETTER.

FOR ADVERSE EVENTS, LOOKING AT ALL THE STUDIES TOGETHER, NONE OF THE COMPARATIVE STUDIES DIRECTLY COMPARED ADVERSE EVENTS. IN GENERAL THEY AT BEST BASICALLY LISTED SOME ADVERSE EVENTS THAT OCCURRED BUT MADE NO ATTEMPT TO COMPARE THE SEVERITY OR OTHER ASPECTS OF THE ADVERSE EVENTS. THE ADVERSE EVENTS THAT WERE FOUND WERE GENERALLY THOSE THAT ONE WOULD EXPECT TO FIND WITH THESE INTERVENTIONS WHICH ARE GENERALLY KNOWN. FOR THE ACE INHIBITORS AND OTHER HYPERTENSIVE AGENTS, THE ADVERSE EVENTS RELATED PRIMARILY TO VASCULAR ADVERSE EVENTS LIKE ORTHOSTATIC HYPOTENSION OR OTHER HYPOTENSION, A KNOWN PHENOMENON,

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AND THEN A SERIES OF OTHER ADVERSE EVENTS, GASTROINTESTINAL, HEADACHES, NAUSEA, THINGS LIKE THAT.

FOR ANGIOPLASTY, THE 30-DAY MORTALITY BETWEEN STUDIES RANGED FROM LESS THAN ONE PERCENT UP TO THREE PERCENT. THERE WAS TRANSIENT ACUTE KIDNEY INJURY THAT OCCURRED BETWEEN ONE AND 13 PERCENT OF PATIENTS WITHIN THE STUDIES. RENAL ARTERY OR PARENCHYMAL INJURY ALSO OCCURRED IN LESS THAN ONE PERCENT OR UP TO 10 PERCENT OF PATIENTS WITHIN STUDIES. THERE WERE ALSO REPORTS OF MAJOR HEMORRHAGE, RENAL ARTERY OCCLUSION AND SPASM, AND FALSE ANEURYSM.

AMONG THE SURGICAL STUDIES, THE 30-DAY MORTALITY WAS HIGHER THAN FOR ANGIOPLASTY, 3.7 TO 9.4 PERCENT. THE PERIOPERATIVE MORBIDITY, IN ONE STUDY IT WAS 16 PERCENT. AND PROCEDURAL COMPLICATIONS, ANOTHER STUDY WAS 22 PERCENT.

SO MOVING ON TO THE SECOND QUESTION, PREDICTORS OF OUTCOMES, 31 STUDIES PROVIDED DATA RELEVANT TO THIS QUESTION. THERE WAS A CONSENSUS THAT SEVERITY OF STENOSIS, POOR KIDNEY FUNCTION, SEVERITY OF COMORBIDITIES, PARTICULARLY SEVERITY OF CARDIOVASCULAR DISEASE, WERE PREDICTORS OF POORER CLINICAL OUTCOMES. THE EXCEPTION TO THIS WAS THE

DRASTIC STUDY, WHICH DID NOT FIND AN ASSOCIATION BETWEEN BASELINE SEVERITY OF STENOSIS AND POORER CLINICAL OUTCOMES. NONE OF THE STUDIES, THOUGH, FOUND THAT ANY OF THESE PREDICTORS ACTUALLY PREDICTED WHICH INTERVENTION WOULD BE BETTER FOR INDIVIDUAL PATIENTS; THIS WAS JUST OVERALL CLINICAL OUTCOMES. THERE WAS LACK OF CONSENSUS WHETHER BILATERAL DISEASE OR AGE OR SEX WERE PREDICTORS OF CLINICAL OUTCOMES. HOWEVER, NOTABLY, AS I DISCUSSED BEFORE, IN THE WEBSTER STUDY, ANGIOPLASTY IN THE SETTING OF BILATERAL DISEASE WAS MORE EFFECTIVE FOR BLOOD PRESSURE CONTROL THAN MEDICAL THERAPY. THIS WAS IN CONTRAST TO THOSE PATIENTS WITH UNILATERAL DISEASE. AND THERE WAS CONSENSUS THAT THERE WAS NO ASSOCIATION BETWEEN BASELINE BLOOD PRESSURE AND PRESENT HYPERTENSION WITH CLINICAL OUTCOMES. REGARDING DIAGNOSTIC TESTS, THERE WERE FOUR DIAGNOSTIC TESTS THAT, WHERE THEY FOUND NO ASSOCIATION BETWEEN THE READING OF THE TESTS AND OUTCOMES. THESE INCLUDED THE CAPTOPRIL TEST, RENOGRAM, ARTERIAL NOREPINEPHRINE, AND UNILATERAL RENIN SECRETION. ONE STUDY DID FIND THAT NONSPIRAL FLOW IN RENAL ARTERIES ON MRA WAS ASSOCIATED WITH PROGRESSION OF KIDNEY DISEASE. THIS WAS A COHORT STUDY SO THERE WAS NO COMPARISON ABOUT HOW THEY WOULD

00042

HAVE DONE WITHOUT THE ANGIOPLASTY.
AND THERE WAS INCONSISTENT RESULTS
REGARDING RESISTIVE INDEX OF OVER 80 PERCENT ON
DOPPLER ULTRASOUND. TWO STUDIES LOOKED AT THIS. ONE
FOUND THAT AN RI OF OVER 80 PERCENT WAS PREDICTIVE OF
WORSENING KIDNEY FUNCTION AND BLOOD PRESSURE CONTROL
AFTER ANGIOPLASTY, COMPARED TO IMPROVEMENT IN THOSE
WITH LOWER RI, BUT THE OTHER STUDY FOUND THAT THERE
WAS POSSIBLY LARGER IMPROVEMENT IN SERUM CREATININE
IN THOSE PATIENTS WITH AN RI OF OVER 80 PERCENT. NO
DIFFERENCE IN THE PERCENTAGE OF PATIENTS WHOSE KIDNEY
FUNCTION DETERIORATED OR IMPROVED BASED ON THEIR RI
READING PRIOR TO THE INTERVENTION.
FOR THE THIRD QUESTION, THERE WERE NO
STUDIES THAT EVALUATED ADJUNCT TREATMENTS OR RELATED
FACTORS AT THE TIME OF ANGIOPLASTY OR SURGERY,
BASICALLY WHAT CO-INTERVENTIONS AT THE TIME OF
SURGERY MIGHT IMPROVE OUTCOMES. HOWEVER, NOTABLY WE
DID NOT DO A COMPARISON, WE DID NOT LOOK AT A
COMPARISON OF ANGIOPLASTY WITH STENT VERSUS
ANGIOPLASTY WITHOUT STENT.
SO THERE ARE A NUMBER OF LIMITATIONS TO
THE EVIDENCE. AS I POINTED OUT, THERE WERE VERY FEW
RANDOMIZED TRIALS. THESE WERE ALSO FELT TO BE OF
LIMITED RELEVANCE TO CURRENT PRACTICE. THERE WERE A

00043

SMALL NUMBER OF PATIENTS, ONLY A HUNDRED PATIENTS TOTAL, FOR THE TIER II EVIDENCE, AND AGAIN, NO RANDOMIZED TRIAL EVALUATING CURRENT TREATMENTS, THERE WAS NO TIER I EVIDENCE. OFTEN THE STUDIES WERE OF POOR QUALITY, HARD TO GET THE OTHER STUDY TYPES. FOR THE MEDICATION COHORT STUDIES, THESE WERE FEW IN NUMBER AND THEY DIDN'T USE THE TRIPLE THERAPY, THE AGGRESSIVE THERAPY OF INTEREST.
THE SMALL NUMBERS AND ITS LIMITATION LIMITS INDIRECT COMPARISON WITH THE STENT COHORTS.
AND ALSO NOTABLY, THE STRICT TYPE OF CRITERIA THAT WE USED FOR THE COHORT STUDIES MAY HAVE ELIMINATED SOME STUDIES THAT MIGHT BE DEEMED IMPORTANT BY SOME EXPERTS IN THE FIELD.
SO THESE ARE OUR CONCLUSIONS. I'M GOING TO READ OUR CONCLUSIONS FROM THE REPORT, BUT GENERALLY THE, OUR FINDINGS WERE THAT THE STUDIES ARE INCONCLUSIVE BECAUSE OF THE SMALL NUMBER OF RANDOMIZED TRIALS WITH FEW PATIENTS AND QUESTIONABLE RELEVANCE TO CURRENT PRACTICE. SORRY. OKAY.
WEAK EVIDENCE SUGGESTS NO DIFFERENCE IN MORTALITY RATES WITH MEDICAL TREATMENT ALONE OR WITH ANGIOPLASTY, THOUGH COMPARATIVE STUDIES WERE TOO SMALL TO ACCURATELY ESTIMATE RELATIVE EFFECT. THERE IS WEAK EVIDENCE SUGGESTING SIMILAR RATES OF

CARDIOVASCULAR EVENTS BETWEEN INTERVENTIONS, ALTHOUGH I DID NOT PRESENT THIS INFORMATION HERE. THERE IS WEAK EVIDENCE SUGGESTING NO DIFFERENCE IN QUALITY OF LIFE WITH MEDICAL TREATMENT ALONE OR WITH ANGIOPLASTY.

THERE IS ACCEPTABLE EVIDENCE THAT OVERALL THERE IS NO DIFFERENCE IN KIDNEY OUTCOMES BETWEEN PATIENTS TREATED MEDICALLY ALONE OR THOSE RECEIVING ANGIOPLASTY WITHOUT STENT, BUT THE RELEVANCE OF THIS FINDING TO CURRENT PRACTICE IS QUESTIONABLE DUE TO CHANGES IN TREATMENT OPTIONS. HOWEVER, IMPROVEMENTS TO KIDNEY FUNCTION WERE ONLY REPORTED AMONG PATIENTS RECEIVING ANGIOPLASTY.

THE EVIDENCE REGARDING THE RELATIVE EFFECT OF ANGIOPLASTY AND MEDICATION ON BLOOD PRESSURE CONTROL IS INCONSISTENT. THE RANDOMIZED TRIALS DID NOT FIND A CONSISTENT EFFECT. OTHER COMPARATIVE STUDIES MOSTLY FOUND NO DIFFERENCE. COHORTS IN MEDICAL TREATMENT GENERALLY FOUND LARGER DECREASES IN BLOOD PRESSURE THAN IN COHORTS OF ANGIOPLASTY WITH STENT. HOWEVER, COHORT STUDIES OF ANGIOPLASTY WITH STENT DID REPORT THAT UP TO 18 PERCENT OF PATIENTS WERE CURED OF HYPERTENSION.

THE EVIDENCE DOES NOT ADEQUATELY ASSESS THE RELEVANT HARMS DUE TO ADVERSE EVENTS AND

COMPLICATIONS OF MEDICAL TREATMENT AND ANGIOPLASTY.
AND THERE IS WEAK EVIDENCE THAT PATIENTS WITH
BILATERAL DISEASE MAY HAVE MORE FAVORABLE OUTCOMES
WITH ANGIOPLASTY THAN WITH MEDICAL THERAPY, COMPARED
TO PATIENTS WITH UNILATERAL DISEASE.
THERE WAS RECURRING CONSISTENT EVIDENCE
THAT DOES NOT SUPPORT WHETHER ANY OTHER CLINICAL
FEATURES OR DIAGNOSTIC TESTS PREDICT OUTCOMES AFTER
ANGIOPLASTY OR WITH MEDICAL THERAPY, AND THERE IS NO
EVIDENCE REGARDING THE VALUE OF PERIPROCEDURAL
INTERVENTIONS WITH ANGIOPLASTY.
SO TO SUMMARIZE, THE EVIDENCE IS LIMITED
TO DIRECT COMPARISONS OF INTERVENTIONS NOT CURRENTLY
IN USE AND SOME INDIRECT COMPARISONS ACROSS COHORT
STUDIES. OVERALL, THE CURRENT EVIDENCE DOES NOT
SUPPORT ONE TREATMENT APPROACH OVER THE OTHER FOR
PATIENTS WITH ATHEROSCLEROTIC RENAL ARTERY STENOSIS.
TWO-THIRDS OF THE STUDIES WERE OF POOR METHODOLOGICAL
QUALITY AND HALF WERE OF LIMITED APPLICABILITY TO THE
POPULATION OF INTEREST. THE ONLY TRIALS WERE SMALL
AND OF POSSIBLY LIMITED RELEVANCE, AND THERE WAS NO
CONSISTENTLY BETTER EFFECT WITH ONE INTERVENTION OVER
ANOTHER.
AMONG THE STUDIES REVIEWED, THE PREDICTIVE
VALUE OF DIAGNOSTIC TESTS EITHER FOR LONG-TERM

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OUTCOMES OR TO HELP DETERMINE THE BEST TREATMENT IS UNCERTAIN.

I DON'T KNOW IF I MENTIONED THIS AT THE BEGINNING, BUT I ALSO WANTED TO STATE THAT I HAVE NO CONFLICTS OF INTEREST. THANK YOU.

DR. GARBER: THANK YOU, DR. BALK. OUR NEXT PRESENTER WILL BE DR. CHRISTOPHER COOPER, FROM THE UNIVERSITY OF TOLEDO.

DR. COOPER: I HAVE BEEN ASKED TO PRESENT THE CASE FOR RENAL ARTERY STENTING FOR TREATMENT OF RENAL ARTERY STENOSIS, AND THIS PRESENTATION IS LARGELY ABSTRACTED FROM A PUBLICATION IN CIRCULATION EARLIER THIS YEAR.

IN TERMS OF DISCLOSURES, I'D LIKE TO DISCLOSE THREE LAYERS OF FINANCIAL INTEREST. ONE IS, I SERVE AS THE PRINCIPAL INVESTIGATOR FOR THE CORAL STUDY FUNDED BY THE NIH. SECONDLY, I HAVE RESEARCH SUPPORT FROM BOTH COMPANIES WHICH SUPPORT RENAL STENTING OR STENT-RELATED PRODUCTS AND FROM COMPANIES WHICH PROVIDE ANTIHYPERTENSIVE MEDICAL THERAPY DIRECTLY RELATED TO PATIENTS WITH ISCHEMIC RENAL DISEASES. AND FINALLY, I WOULD LIKE TO DISCLOSE THAT I DO HAVE PATIENT CARE-RELATED CONFLICTS OF INTEREST SINCE I DO RENAL INTERVENTIONAL PROCEDURES, AND I AM ALSO INVOLVED IN THE MEDICAL MANAGEMENT OF PATIENTS

WITH ISCHEMIC RENAL SYNDROMES. FINALLY, I HAVE BEEN INCLUDED IN DISCUSSIONS WITH SCA&I ABOUT THEIR RESPONSE TO CMS'S POLICY REVIEW AND EXPRESSED MY OPINIONS ON THE MATTER TO SCA&I.

RENAL ARTERY STENOSIS IS A COMMON PROBLEM IN REGARD TO THE ELDERLY CMS POPULATION. KEN HANSEN FROM WAKE HAS DEMONSTRATED NICELY THAT IN AN UNSELECTED GROUP, ABOUT SEVEN PERCENT OF FOLKS IN THE UNITED STATES HAVE SIGNIFICANT ISCHEMIC RENAL DISEASE, SO THIS IS A QUITE RELEVANT POPULATION. THE MAJORITY OF ATHEROSCLEROTIC STENOSES ARE OSTIAL NARROWINGS WHICH ARE ATTRIBUTED OFTENTIMES TO EXTENSION OF AORTIC PLAQUE INTO THE OSTIA OF THE RENAL ARTERY. AS A CONSEQUENCE, THEY OFTEN OCCUR IN THE SETTING OF A HIGHLY DISEASED AORTA AND THEY MAY BE UNILATERAL, THEY MAY BE BILATERAL, OR THEY MAY BE INVOLVING A SOLITARY FUNCTIONING KIDNEY.

IN TERMS OF THE EFFECT OF RENAL ARTERY STENOSIS ON HYPERTENSION, THERE HAS BEEN SOME DISCUSSION IN THE PAST AS TO WHETHER IT DOES CAUSE HYPERTENSION. I THINK THERE IS NO DOUBT THAT A STENOSIS CAN CAUSE HYPERTENSION. HOWEVER, IT MAY BE DIFFICULT IN AN INDIVIDUAL PATIENT TO ASCERTAIN WHETHER THEIR HYPERTENSION PER SE IS ATTRIBUTABLE TO THE STENOSIS OR TO SOME CONFOUNDING EFFECT SUCH AS

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ESSENTIAL HYPERTENSION.
WHAT IS KNOWN BIOLOGICALLY IS THAT DECLINE
IN PRESSURE WITHIN THE RENAL ARTERY IS SENSED AT THE
JUXTAGLOMERULAR APPARATUS WHICH STIMULATES RELEASE OF
RENIN. RENIN CATALYZES CONVERSION OF ANGIOTENSINOGEN
TO A I. AND A II NOT ONLY IS A HYPERTENSIVE AGENT,
BUT IT ALSO PROMOTES ALDOSTERONE RELEASE FROM THE
ADRENAL CORTEX, FURTHER INCREASING THE HYPERTENSIVE
RESPONSE.
HOWEVER, THERE HAVE BEEN A NUMBER OF OTHER
MEDIATORS IDENTIFIED OVER THE PAST 10 OR 15 YEARS
WHICH HELP PERPETUATE THAT HYPERTENSION IS RELATED TO
RENAL ARTERY STENOSIS, INCLUDING SYMPATHETIC
ACTIVATION, RELEASE OF REACTIVE OXYGEN SPECIES,
CONTRALATERAL NEPHROSCLEROSIS, ENDOTHELIAL
DYSFUNCTION WHICH MAY BE IMPORTANT, BUT THEN
INTERESTINGLY SECONDARY HYPERALDOSTERONISM, WHICH
SOME THINK MAY BE DUE TO THIS CHRONIC STIMULATION OF
ALDOSTERONE RELEASE.
A FEW WORDS ABOUT RENAL ARTERY STENOSIS
AND KIDNEY FUNCTION. RENAL ARTERY STENOSIS IS AN
UNCOMMON CAUSE OF KIDNEY FAILURE PER SE. THERE WAS
SOME INTEREST 15 OR 20 YEARS AGO THAT RENAL ARTERY
STENOSIS IS A CAUSE OF END-STAGE RENAL DISEASE. I
THINK PEOPLE HAD TROUBLE REPLICATING IT AS A COMMON

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CAUSE OF END-STAGE RENAL DISEASE. HOWEVER, RENAL INSUFFICIENCY IS COMMON IN PATIENTS WITH RENAL ARTERY STENOSIS, AND THE POTENTIAL MEDIATORS MAY BE HEMODYNAMIC OR RELATED TO HYPOPERFUSION OF THE KIDNEYS. THEY MAY BE RELATED TO THE TOXIC EFFECTS OF RENIN, ANGIOTENSIN II, ENDOTHELIUM OR TGF BETA DIRECTLY ON THE KIDNEY. AT THE LEVEL OF THE RENAL TUBULE THERE IS GOOD BASIC EVIDENCE THAT TUBULAR NECROSIS OCCURS AND PROGRAMMED CELL DEATH OCCURS IN HYPOPERFUSED KIDNEYS. BUT IMPORTANTLY, THERE ARE OTHER CONFOUNDING CAUSES IN INDIVIDUAL PATIENTS WHICH MAKE IT DIFFICULT TO ASCERTAIN WHETHER THE STENOSIS PER SE OR SOMETHING ELSE IS LEADING TO DYSFUNCTION, AND THESE INCLUDE ESSENTIAL HYPERTENSION, DIABETES, ATHEROEMBOLISM, AND ADVANCING AGE IN MANY OF OUR PATIENTS.

ONE OF THE HALLMARKS OF THIS DISORDER IS THAT IT'S ASSOCIATED WITH POOR SURVIVAL. THERE HAVE BEEN A NUMBER OF STUDIES WHICH HAVE LOOKED AT SURVIVAL IN PATIENTS WITH ISCHEMIC KIDNEY DISEASE, THIS IS PROBABLY THE BEST, BY CONLON, USING THE DUKE DATABASE. THIS IS FOUR-YEAR SURVIVAL. IF YOU DON'T HAVE RENAL ARTERY STENOSIS, YOU HAD ABOUT A 90 PERCENT FOUR-YEAR SURVIVAL; IF YOU DID HAVE RENAL ARTERY STENOSIS, YOUR SURVIVAL WAS LESS, AT ABOUT 57

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PERCENT.
IMPORTANTLY, THOUGH, THERE WAS A GREAT EFFECT OF STENOSIS BEARING ON SURVIVAL, WHICH IS TO SAY THE MORE SEVERE YOUR LESION, THE MORE LIKELY YOU ARE TO HAVE A FATAL EVENT. THE CHALLENGE WITH THIS TYPE OF OBSERVATION, THOUGH, IS WHETHER THIS IS A CAUSAL RELATIONSHIP, I.E., ARE THESE STENOSES CAUSING PEOPLE TO HAVE FATAL EVENTS, OR IS THIS SIMPLY A GOOD MARKER OF RISK FOR ADVANCED ATHEROSCLEROSIS AND THE RISK FACTORS WHICH LEAD TO ATHEROSCLEROSIS, INCLUDING DIABETES, ESSENTIAL HYPERTENSION, ET CETERA.
ONE OF THE IMPORTANT RELATIONSHIPS THAT HAS BEEN IDENTIFIED RECENTLY IS THAT BETWEEN ISCHEMIC RENAL DISEASE AND CLINICAL EVENTS. A FEW YEARS AGO WE LOOKED AT TWO DATA SETS, ONE WAS A LARGE SINGLE SENTRY COHORT, THE SECOND WAS A LARGE MULTICENTER FDA-APPROVAL TRIAL, TO TRY TO UNDERSTAND WHAT HAPPENS TO PATIENTS WITH ISCHEMIC RENAL DISEASE. AND INTERESTINGLY, AT A MEDIAN TWO-YEAR FOLLOW-UP, ABOUT ONE-THIRD OF THE PATIENTS DIDN'T EXPERIENCE AN ADVERSE EVENT. DESPITE A STRONG ASSOCIATION WITH RENAL FUNCTION, 90 PERCENT OF THE ADVERSE EVENTS ARE NOT RENAL EVENTS, THEY'RE CARDIOVASCULAR EVENTS.
AND HERE'S A DEPICTION OF THE RELATIONSHIP BETWEEN RENAL DISEASE AND THE PROBABILITY OF AN

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EVENT. AGAIN, THIS IS RELATIVELY SHORT-TERM FOLLOW-UP, BUT AS YOU CAN SEE, IF YOU HAVE AN ESTIMATED GFR WHICH IS QUITE LOW, YOUR RISK OF FATAL EVENT MAY BE AS HIGH AS 60 PERCENT, THE MAJORITY OF WHICH ARE CARDIOVASCULAR AND RENAL. HOWEVER, IF WE LOOK AT THE ACTUAL EVENTS WHICH ARE OCCURRING IN THIS POPULATION AND LOOK AT THE TIME TO FIRST EVENT, THE FIRST EVENT IS THE FATAL EVENT IN ABOUT A THIRD OF THE PATIENTS, CONGESTIVE HEART FAILURE IN ABOUT A THIRD OF THE PATIENTS, MYOCARDIAL INFARCTION ABOUT 13 PERCENT, STROKE IN EIGHT PERCENT, DOUBLING OF CREATININE IN ABOUT SEVEN PERCENT, RENAL REPLACEMENT THERAPY IN THREE PERCENT. SO AGAIN, DESPITE THE STRONG RELATIONSHIP BETWEEN ADVANCED RENAL DISEASE AND ADVERSE EVENTS, THE MAJORITY OF THEM ARE NOT RENAL EVENTS PER SE, THEY ARE CARDIOVASCULAR EVENTS. WELL, THE REAL QUESTION, OR ONE OF THE IMPORTANT QUESTIONS TO CONSIDER IS, IS THIS AN ISSUE OF ASSOCIATION OR CAUSATION? I'D LIKE TO SUGGEST THAT IN A VERY ATTRACTIVE HYPOTHESIS, THAT IN FACT THESE STENOSES ARE LEADING TO HIGH RATES OF ADVERSE EVENTS. WE START WITH A MILIEU OF ATHEROSCLEROSIS WE TALKED ABOUT IN THE ABDOMINAL AORTA. WE ADD THE EFFECT OF NEUROENDOCRINE ACTIVATION. THE STENOSIS LEADS TO HYPOPERFUSION OF THE KIDNEYS. AS WE'VE

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ALREADY DISCUSSED, THERE'S ACTIVATION OF THE NEUROENDOCRINE SYSTEM INCLUDING RENIN, ANGIOTENSIN, SYMPATHETIC ACTIVATION, WHICH LEADS TO CONTRALATERAL NEPHROSCLEROSIS, VENTRICULAR HYPERTROPHY, ACCELERATION OF ATHEROSCLEROSIS AND CHANGES IN THE BRAIN.

AND THEN WE FINALLY ADD ON TOP OF THAT THE UNIQUE RISK FACTOR OF CHRONIC KIDNEY DISEASE.

THERE'S BEEN A LOT OF INTEREST IN THE PAST FIVE YEARS OR SO ABOUT HOW CHRONIC KIDNEY DISEASE LEADS TO CARDIAC VASCULAR EVENTS. ENDOTHELIAL DYSFUNCTION IS RELATED TO ASYMMETRIC LARGENING, MEDIAL CALCIFICATION. A NUMBER OF FACTORS HAVE BEEN PROPOSED AS MECHANISMS WHEREBY CKD LEADS TO EVENTS, BUT CERTAINLY THIS MAY BE A VERY UNFAVORABLE NEW VIEW OF ATHEROSCLEROSIS, NEUROENDOCRINE ACTIVATION AND CKD.

DOES MEDICAL THERAPY HAVE LIMITATIONS?

PROBABLY SO. THERE MAY BE LAPSES IN MEDICAL THERAPY RELATED TO COMPLIANCE AND COSTS. WE KNOW FROM ENHANE'S DATA THAT ONLY HALF THE PATIENTS WHO ARE HYPERTENSIVE TAKE THEIR MEDICINE, MOST AREN'T CONTROLLED. WE KNOW THAT ANTIHYPERTENSIVE THERAPIES HAVE SIDE EFFECTS WHICH MAY BE SIGNIFICANT IN THE ELDERLY POPULATION. IT'S AT LEAST THEORETICALLY

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POSSIBLE THAT THERE COULD BE CONTINUED PROGRESSION OF CKD DUE TO CHRONIC RENAL ISCHEMIA. AND FINALLY, IT'S NOT CLEAR WHAT THE LONG-TERM EFFECTS OF ACTIVATION OF THE RENIN-ANGIOTENSIN SYSTEM OR THE SYMPATHETIC ACTIVATION ARE ON CARDIOVASCULAR OUTCOMES INDEPENDENT OF BLOOD PRESSURE CONTROL.

ALL RIGHT. SO WHAT'S THE EVIDENCE BASE FOR RENAL INTERVENTION? WELL, I THINK THIS HAS BEEN COVERED AND I'M JUST GOING TO TRY TO GIVE AN OVERVIEW OF WHAT I THINK ARE THE IMPORTANT DEVELOPMENTS IN THE FIELD. BUT SIMPLY PUT, EARLY HISTORICALLY-CONTROLLED WORK SUGGESTED IMPROVED SURVIVAL IN SURGICALLY REVASCULARIZED PATIENTS. HOWEVER, THIS OBSERVATION WAS LIMITED BY PATIENT SELECTION AND WOLLENWEBER AND HUNT BOTH SAID THAT A CONTROLLED RANDOMIZED TRIAL NEEDED TO BE PERFORMED IN ORDER TO ASSERT WHETHER THIS EFFECT WAS REAL OR NOT.

IMPORTANTLY, ANGIOPLASTY WITHOUT STENTING AND SURGERY APPEAR EQUIVALENT FOR BLOOD PRESSURE CONTROL AND RENAL FUNCTION. THIS WAS A RANDOMIZED TRIAL PUBLISHED IN 1993. HOWEVER, SURGICAL REVASCULARIZATION HAD SIGNIFICANTLY MORE MAJOR COMPLICATIONS, 34 VERSUS 17 PERCENT, DESPITE THE ABILITY OF SURGERY TO ACHIEVE A HIGHER PRIMARY PATENCY RATE. AND THESE AUTHORS RECOMMENDED

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ANGIOPLASTY AS A PRIMARY TREATMENT STRATEGY BECAUSE IT AVOIDED THE HIGH MORTALITY AND MORBIDITY EARLY ON ASSOCIATED WITH SURGERY, AND LARGELY THAT WAS A TRANSITION POINT.

AS HAS BEEN ALLUDED TO, THERE HAVE BEEN THREE RANDOMIZED TRIALS OF ANGIOPLASTY CONTRASTED TO MEDICAL THERAPY, WHICH WERE NEGATIVE FOR THEIR PRIMARY ENDPOINTS OF BLOOD PRESSURE CONTROL. AGAIN, WE'VE HEARD THAT THESE DID NOT INCLUDE STENT, THERE WERE HIGHER RATES OF CROSSOVER, AND THE FOLLOW-UP TENDED TO BE RELATIVELY SHORT TERM. AND FINALLY, THE SAMPLE SIZES WERE FRANKLY INADEQUATE TO DETECT A MEANINGFUL DIFFERENCE IN BLOOD PRESSURE CONTROL.

SUBSEQUENTLY IT'S BEEN DEMONSTRATED THAT STENTING IS SUPERIOR TO ANGIOPLASTY FOR THE MAJORITY OF ATHEROSCLEROTIC STENOSES FOR THE PREVENTION OF RESTENOSIS. THIS WAS PUBLISHED BY VAN DER VEN IN LANCET IN 1999. AND THUS, STENTING HAS BECOME THE DOMINANT MODE OF REVASCULARIZATION. IMPORTANTLY, THOUGH, OUR CURRENT GENERATION OF FDA APPROVAL TRIALS FOCUS ON DEVICE PERFORMANCE SPECIFIC TO THIS RATE OF RESTENOSIS RATED AGAINST ANGIOPLASTY, WHICH I WOULD SUGGEST TO YOU IS NOW A TREATMENT OF HISTORICAL RELEVANCE. SO THE STRATEGY IS TO TREAT FAILED BALLOON ANGIOPLASTY, CONTRAST RESTENOSIS RATES

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AGAINST SOME OBJECTIVE PERFORMANCE CRITERIA. THE CHALLENGE IS THAT FOR CLINICIANS, THESE TYPES OF STUDIES PROVIDE LITTLE INFORMATION ABOUT DECISION-MAKING FOR PATIENT CARE, ALTHOUGH THEY MAY PROVIDE FDA WITH VALUABLE INFORMATION ABOUT RESTENOSIS RATES PER SE RELATED TO A DEVICE.

FINALLY, AS HAS BEEN ALLUDED TO, THERE ARE A NUMBER OF SINGLE CENTER CASE REPORTS AND COHORT STUDIES OF STENTING. BROADLY THEY CAN BE LUMPED AS DEMONSTRATING BENEFIT FOR RENAL FUNCTION. HARDEN IN LANCET, WATSON IN CIRCULATION, DEMONSTRATED THAT INFLECTION IN THE SLOPE OF RECIPROCAL CREATININE OCCURS. OTHER PEOPLE HAVE DEMONSTRATED SIMILAR FINDINGS, THOUGH, IN MEDICALLY TREATED PATIENTS. AS HAS BEEN ALLUDED TO, BLOOD PRESSURE CONTROL APPEARS TO BE IMPROVED AFTER STENTING, BUT THIS HAS ALSO BEEN DEMONSTRATED IN PATIENTS WITH MEDICAL THERAPY, WHICH REMAINS CONSISTENT, WHICH IS TERMED A CLINICAL OBSERVATIONAL EFFECT.

I WOULD LIKE TO DIGRESS A MOMENT ON WHAT I THINK IS SOME OF THE CONFUSION ABOUT THE EFFECT OF REVASCULARIZATION ON RENAL FUNCTION, AND I'LL EMBARRASS STEVE TEXTOR FOR THIS IMPORTANT PANEL TAKEN FROM A PUBLICATION HE HAD DONE IN AMERICAN SOCIETY OF NEPHROLOGY A FEW YEARS BACK, WHICH IS LOOKING AT

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SURGICAL REVASCULARIZATION, BUT I REALLY THINK THAT THERE'S IMPORTANT INFORMATION HERE. IF YOU LOOK AT PATIENTS UNDERGOING REVASCULARIZATION, WHAT YOU SEE IS THE FOLLOWING: ABOUT A QUARTER OF THE PATIENTS HAVE A SIGNIFICANT IMPROVEMENT IN RENAL FUNCTION. ABOUT HALF THE PATIENTS HAVE STABLE RENAL FUNCTION AND ABOUT ONE IN FIVE HAVE A SIGNIFICANT INCREASE IN THEIR SERUM CREATININE. THIS HAS MEANING IN TWO -- THIS FINDING OBVIOUSLY, I WOULD SUGGEST TO YOU, IS ALSO CONSISTENT WITH WHAT IS OBSERVED WITH STENT REVASCULARIZATION. IF WE LOOK AT THE PUBLISHED DATA FROM ASPIRE II, WHICH WAS AN FDA APPROVAL REGISTRY, IF WE LOOK AT THE CHANGE IN SERUM CREATININE OVER TIME, 1.4, 1.4, 1.5, A NEGLIGIBLE CHANGE, BUT IMPORTANTLY WHAT ONE OBSERVES IS THAT THE STANDARD DEVIATION TERM CONTINUES TO BROADEN, WHICH SUGGESTS THAT THERE ARE PATIENTS THAT ARE GETTING BETTER, PATIENTS THAT ARE GETTING WORSE, AND PATIENTS THAT AREN'T CHANGED. AND AS A CONSEQUENCE WHEN YOU SPEAK TO PROVIDERS OF THIS THERAPY, OFTENTIMES PEOPLE WILL RECOUNT THE ONE OR TWO PATIENTS THAT GOT SIGNIFICANTLY BETTER AND MAY MAKE THE CLAIM THAT I THINK STENTING IS AN EXCELLENT THERAPY AND EVERYBODY SHOULD GET IT. ALTERNATIVELY, IF YOU'RE A

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NEPHROLOGIST IN PRACTICE, THE PATIENTS YOU'RE LIKELY TO BE REFERRED TO ARE THOSE WHOSE RENAL FUNCTION DECLINES AND REQUIRE DIALYSIS. AND SO AS A CONSEQUENCE, WHAT I WOULD SUGGEST TO YOU IS THAT THE ONE THING THAT WE HAVE LEARNED ABOUT THE THERAPIES OF REVASCULARIZATION IS THAT THERE IS DIVERGENCE OF OUTCOME OVER TIME AND BLUNTLY, IT'S HARD TO PREDICT WHO'S GOING TO DO BETTER AND WHO IS NOT GOING TO DO BETTER.

WELL, IF RENAL ARTERY STENOSIS IS ASSOCIATED WITH NEUROHUMORAL ACTIVATION AND POOR OUTCOMES, AND CAN CAUSE HYPERTENSION AND CHRONIC KIDNEY DISEASE, WHY DO WE NEED MORE STUDIES? I'LL SAY WITH SOME DEGREE OF CERTAINTY THAT ALL PATIENTS WITH RENAL ARTERY STENOSIS NEED EFFECTIVE MEDICAL THERAPY, THEY NEED TO BE ON ANTIHYPERTENSIVES, THEY NEED TO BE ON STATINS, THEY NEED TO BE ON ANTIPLATELET THERAPY, THEY NEED TO HAVE THEIR GLUCOSE CONTROLLED IF THEY'RE DIABETIC. ALL THESE INTERVENTIONS HAVE BEEN PROVEN IN RANDOMIZED TRIALS. THE ISSUE IS, ARE THE OUTCOMES ATTRIBUTABLE TO RENAL ARTERY STENOSIS, AND DOES STENTING CHANGE THE OUTCOME WHEN ADDED TO THE EFFECT OF MEDICAL THERAPY. AS A CONSEQUENCE, IF YOU TRAVEL AROUND THE UNITED STATES, WHICH I HAVE HAD THE

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PLEASURE TO DO AS PART OF THE CORAL STUDY LEADERSHIP TEAM, WE'VE NOW VISITED APPROXIMATELY 80 MEDICAL CENTERS INSIDE THE UNITED STATES WHO ACTIVELY CARE FOR THESE PATIENTS, WHAT YOU SEE IS BROAD DIVERGENCE IN THE OPINIONS OF MEDICAL EXPERTS. AND THIS MAY SEEM SILLY, BUT WITHIN THE INTERNAL MEDICINE COMMUNITY AND NEPHROLOGY COMMUNITY, THE GENERAL VICTIM IS SCREENED RARELY AND STENTED EVEN LESS BECAUSE OF CONCERNS ABOUT PATIENTS WITH DECLINING RENAL FUNCTION AFTER THE PROCEDURE AND WHETHER THESE THERAPIES ACTUALLY DO IMPROVE BLOOD PRESSURE CONTROL OR RENAL FUNCTION.
IN CONTRAST, IF YOU SPEAK TO INVESTIGATORS WHO ARE SURGEONS OR INTERVENTIONAL CARDIOLOGISTS OR INTERVENTIONAL RADIOLOGISTS, QUITE OFTEN THERE'S A COMPULSION TO TREAT EVERYBODY, BECAUSE IF WE DON'T, THE PATIENT'S KIDNEY FUNCTION MAY GET WORSE. AND THE CONSEQUENCE WHICH I THINK IS SOMEWHAT TROUBLING IS THAT THE TYPE OF CARE YOU RECEIVE MAY BE MORE DICTATED BY THE SPECIALTY AFFILIATION OF THE GUY YOU SHOW UP TO SEE RATHER THAN THE MEDICAL CONDITION THAT YOU ACTUALLY HAVE.
FINALLY, I'VE BEEN ASKED BY --
DR. GARBER: EXCUSE ME. DR. COOPER, I'M GOING TO HAVE TO ASK YOU TO WRAP UP.

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DR. COOPER: OKAY, VERY GOOD. I'VE BEEN ASKED BY CMS TO BRIEFLY GIVE AN OVERVIEW OF CORAL. THERE IS A RANDOMIZED TRIAL OF PATIENTS WITH RENAL ARTERY STENOSIS WHO ARE RANDOMIZED TO STENT OR NO STENT. THEY ARE GIVEN OPTIMAL MEDICAL THERAPY INCLUDING A STATIN, ANGIOTENSIN RECEPTOR BLOCKER, ET CETERA. THE PRIME ENDPOINT IS CLINICAL EVENT. IT SHOULD BE POWERED ADEQUATELY TO DETECT CLINICAL EVENTS.

CMS HAS ASKED ME TO TALK ABOUT ENROLLMENT IN CORAL. RIGHT NOW WE'RE ON OUR REVISED TARGET. ENROLLMENT WAS SLOW AT THE BEGINNING, ALTHOUGH IT HAS IMPROVED.

IN ADDITION, THEY HAVE ASKED FOR AN OPINION ABOUT OR EVIDENCE ABOUT THE IMPACT OF U.S. AND NON-U.S. ENROLLMENT. AS ONE CAN SEE, U.S. ENROLLMENT HAS IMPROVED OVER TIME AND ENROLLMENT OUTSIDE THE U.S. HAS RECENTLY INCREASED. THE ISSUE OF OUS ENROLLMENT IS AN INTERESTING ONE. IT HELPS US ACHIEVE OUR OVERALL ENROLLMENT OBJECTIVE BUT DOES LIMIT THE REPRESENTATION OF THE U.S. POPULATION AND LESSENS APPLICABILITY TO THE U.S. HEALTHCARE SYSTEM.

SO THE CASE FOR RENAL ARTERY STENTING IS, ISCHEMIC RENAL DISEASE IS ASSOCIATED WITH POOR OUTCOMES. STENTING IS THE APPROPRIATE DOMINANT MODE

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OF REVASCULARIZATION. IT HAS A LOT OF PROMISE BUT THE ROLE IN ADDITION TO MEDICAL THERAPY REMAINS UNCLEAR, AS HAS BEEN DISCUSSED PREVIOUSLY, AND CORAL IS DESIGNED TO ADDRESS THIS QUESTION. HOWEVER, YOU'RE NOT GOING TO HAVE AN ANSWER FOR SEVERAL YEARS AND A DEFINITIVE RESULT WILL DEPEND ON ACHIEVING ADEQUATE ENROLLMENT.

DR. GARBER: THANK YOU, DR. COOPER. NEXT, DR. DWORKIN.

DR. DWORKIN: I'M LANCE DWORKIN, THE STUDY CHAIR FOR THE CORAL TRIAL. I WORK CLOSELY WITH CHRIS COOPER ON THAT. I'M ALSO A NEPHROLOGIST AT BROWN MEDICAL SCHOOL AND I WAS ASKED TO PRIMARILY PRESENT THE ARGUMENTS FROM AN ARTICLE THAT APPEARED AS A COMPANION TO THE ONE CHRIS WROTE IN CIRCULATION, MAKING A CASE AGAINST ANGIOPLASTY AND STENTING.

BY WAY OF DISCLOSURES UNDER THE CORAL TRIAL, I DON'T FEEL I HAVE ANY SIGNIFICANT CONFLICTS OF INTEREST.

A LOT OF THE DATA THAT YOU'RE GOING TO SEE FROM ALL OF US, I THINK, IS A LITTLE BIT REPETITIVE BECAUSE WE'RE ALL OPERATING FROM THE SAME MEAGER DATABASE, WHICH HOPEFULLY WILL JUST ALLOW ME TO MOVE QUICKLY. I THINK THE POINT OF THIS SLIDE IS THAT THIS IS A COMMON PROBLEM IN THE ELDERLY POPULATION,

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AND IT'S PARTICULARLY COMMON IN PEOPLE THAT HAVE VASCULAR DISEASE IN OTHER BEDS, SO PERIPHERAL VASCULAR DISEASE, CORONARY ARTERY DISEASE AND CEREBRAL VASCULAR DISEASE.

CHRIS ALREADY SHOWED YOU SOME OF THIS DATA ON OUTCOMES. THESE PATIENTS ARE ILL. THESE ARE SOME OF THE COMMON COMORBIDITIES SEEN IN PATIENTS WITH RENOVASCULAR DISEASE. UNCONTROLLED OR SEVERE HYPERTENSION IS THE MOST COMMON COMPLAINT.

PREVALENCE OF DIABETES IS ABOUT 20 PERCENT. MOST HAVE A SMOKING HISTORY, EITHER CURRENT OR REMOTE.

THERE'S THE CONCORDANCE WITH OTHER VASCULAR DISEASE.

AND IN OUR OWN SERIES OF PATIENTS AT BROWN, ABOUT 50 PERCENT OF THE PATIENTS PRESENT ALREADY WITH SOME DEGREE OF RENAL INSUFFICIENCY.

I THINK THE IMPORTANT THING FOR ME AS A NEPHROLOGIST IS THAT ALTHOUGH PROGRESSION TO END-STAGE RENAL DISEASE OR PRESERVING KIDNEY FUNCTION IS OFTEN GIVEN AS AN ARGUMENT FOR PERFORMING RENAL INTERVENTION, ACTUALLY OVER AT LEAST A COUPLE YEARS OF FOLLOW-UP, THE NUMBER OF PATIENTS THAT PRESENT AND PROGRESS TO END-STAGE RENAL DISEASE ASSOCIATED WITH RENOVASCULAR DISEASE IS ACTUALLY VERY SMALL.

CHRIS ALREADY MENTIONED THE SURVIVAL DATA, THAT RENAL ARTERY STENOSIS ADVERSELY AFFECTS SURVIVAL

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IN CASES OF CORONARY ARTERY DISEASE, AND HE SHOWED YOU THIS SLIDE BUT NOT THIS ONE, WHICH REALLY SHOWS THE IMPACT OF INCREASING SEVERITY OF STENOSIS ON OUTCOMES AND AS THE DEGREE OF STENOSIS INCREASES, SURVIVAL OVER FIVE YEARS HERE DECREASES.

SO WHAT IS THE EXPLANATION FOR THE HIGH ADVERSE EVENT RATE IN PATIENTS WITH RENAL ARTERY STENOSIS? AND THIS WAS ALREADY MENTIONED, THIS NOTION THAT THERE IS NEUROHUMORAL ACTIVATION, ACTIVATION OF THE RENIN/ANGIOTENSIN/ALDOSTERONE SYSTEM, SYMPATHETIC NERVOUS SYSTEM MAY BE DRIVING THESE OUTCOMES. I THINK IT'S HARD TO KNOW, HOWEVER, HOW THIS PLAYS OUT IN TERMS OF WHICH THERAPEUTIC INTERVENTION WILL BE BETTER, BECAUSE WHILE YOU MAY BE ABLE TO REVERSE SOME OF THESE CHANGES BY OPENING THE RENAL ARTERY, WE ALSO HAVE EFFECTIVE MEDICAL INTERVENTIONS, DRUGS THAT CAN BLOCK THESE SYSTEMS.

THE ASSOCIATION BETWEEN REN VASCULAR DISEASE AND RENAL FUNCTION, AND THE FACT THERE IS INCREASING EVIDENCE AT LEAST THAT IN PATIENTS WITH CHRONIC KIDNEY DISEASE, THEY HAVE AN INCREASED RISK FOR CARDIOVASCULAR DISEASE. AND THEN THERE IS THIS POSSIBILITY, AND THAT IS THAT THE ADVERSE OUTCOME IS JUST A CONSEQUENCE OF THE FACT THAT BY THE TIME THESE PATIENTS ARE IDENTIFIED, THEY ALREADY HAVE DIFFUSE

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SEVERE ATHEROSCLEROTIC DISEASE, AND YOU MIGHT SUSPECT THAT IN THIS CONTEXT, FIXING A LESION IN A SINGLE BLOOD VESSEL MIGHT NOT HAVE THAT DRAMATIC OF IMPACT. SO THESE ARE THE MOST COMMON JUSTIFICATIONS GIVEN FOR INTERVENING IN RENAL ARTERY STENOSIS, AND I USE THE WORD JUSTIFICATIONS RATHER THAN INDICATIONS BECAUSE AS YOU'VE ALREADY HEARD, THERE REALLY ISN'T GOOD EVIDENCE THAT THESE OUTCOMES ARE IMPROVED BY INTERVENTIONS. SO RESISTANT HYPERTENSION IS PROBABLY THE MOST COMMON JUSTIFICATION. TO STABILIZE OR PREVENT PROGRESSION TO END-STAGE RENAL DISEASE IN PATIENTS WITH EITHER DECLINING OR IMPAIRED KIDNEY FUNCTION, WHICH IS COMMON. AND THEN ANOTHER COMMON JUSTIFICATION ARE TO REDUCE THE SEVERITY OR ADMISSIONS FOR CONGESTIVE HEART FAILURE.

SO WHAT'S THE EVIDENCE FOR THIS? AGAIN, YOU'VE ALREADY SEEN THESE TRIALS SUMMARIZED AND I WON'T BELABOR THIS. THESE ARE THE THREE RANDOMIZED CONTROLLED TRIALS. THEY HAD VARIOUS PROBLEMS. SUFFICE IT TO SAY THAT THERE REALLY HASN'T BEEN, EXCEPT IN THIS ONE STUDY OF BILATERAL DISEASE WITH A RELATIVELY SMALL NUMBER OF PATIENTS HERE, A SIGNIFICANT DIFFERENCE IN BLOOD PRESSURE IN THE RANDOMIZED CONTROLLED TRIALS OF PATIENTS TREATED

MEDICALLY VERSUS THOSE TREATED WITH REVASCULARIZATION.

IN ALL OF THESE STUDIES THERE IS A TENDENCY FOR THE NUMBER OF DRUGS REQUIRED TO CONTROL BLOOD PRESSURE TO DECLINE. THESE PATIENTS ALWAYS REQUIRE MULTIPLE DRUGS TO CONTROL THEIR BLOOD PRESSURE, TYPICALLY THREE, FOUR, FIVE MEDICATIONS, AND ON AVERAGE THE NUMBER OF MEDICATIONS NEEDED DECLINES BY ABOUT ONE MEDICATION. WHETHER OR NOT THAT'S A CHANGE THAT WOULD BE ASSOCIATED WITH SIGNIFICANTLY BETTER OUTCOMES FOR PATIENTS, I DON'T THINK IS KNOWN.

WHAT ABOUT THE EFFECTS OR WHY ISN'T REVASCULARIZATION BETTER AS A TREATMENT FOR HYPERTENSION? WELL, ONE OF THE PROBLEMS I THINK IS ILLUSTRATED BY THIS. THIS IS ACTUALLY AN ANIMAL MODEL, THE GOLDBLATT HYPERTENSIVE MODEL OF ONE KIDNEY, OR TWO KIDNEYS, WITH HYPERTENSION. AND THIS IS A STUDY IN RATS WHICH LOOKS AT THE EFFECTS OF UNCLIPPING THE RENAL ARTERY, SO ESSENTIALLY DOING ANGIOPLASTY IN RATS THAT HAVE HYPERTENSION AS A RESULT OF CONSTRICTING THE RENAL ARTERY EITHER AT THREE MONTHS OF HYPERTENSION OR AT SIX MONTHS OF HYPERTENSION.

AND WHAT YOU CAN SEE IS THAT IF YOU

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REVASCULARIZE EARLY, THAT HYPERTENSION IN FACT IMPROVES AND IS CURED. HOWEVER, IF YOU REVASCULARIZE LATE, THE HYPERTENSION IS SUSTAINED, EVEN THOUGH THE RENAL ARTERY LESION IS NO LONGER HERE. AND WHAT IS THE EXPLANATION FOR THAT? WELL, THERE ARE PROBABLY A NUMBER OF FACTORS; SOME OF THESE FACTORS ARE VASCULAR, CHANGES IN ARTERIAL THICKENING AND ENDOTHELIAL DYSFUNCTION THAT TENDS TO SUSTAIN HYPERTENSION. AND THEN A MAJOR PROBLEM IS PROBABLY UNDERLYING KIDNEY DISEASE IN THESE PATIENTS, AND THIS IS KIDNEY DISEASE THAT IS NOT DIRECTLY RELATED TO THE RENAL ARTERY STENOSIS.
HYPERTENSIVE NEPHROSCLEROSIS IN PATIENTS WITH UNILATERAL DISEASE, THE KIDNEY THAT'S NOT DISTAL TO A STENOSIS IS EXPOSED TO HIGH PERFUSION PRESSURES AND IS INJURED, AND THEN WHAT WE CALL ISCHEMIC NEPHROPATHY IN THE KIDNEY THAT'S DISTAL TO THE STENOSIS, WHERE THERE'S ACTIVATION OF CYTOKINES AND INFLAMMATION AND FIBROSIS AS WELL. AND ONCE YOU HAVE SEVERE RENAL FUNCTIONAL IMPAIRMENT, EVEN IF YOU OPEN UP THE ARTERY, THAT'S UNLIKELY TO IMPROVE HYPERTENSION SIGNIFICANTLY. AND THIS IS ALSO RELEVANT TO THE CHANGES IN KIDNEY FUNCTION.
AND AGAIN, YOU'VE ALREADY SEEN THIS SLIDE
AND AS A NEPHROLOGIST, MY INTERPRETATION OF THIS DATA

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IS THAT IF YOU REVASCULARIZE PATIENTS THAT HAVE RENAL ARTERY STENOSIS AND IMPAIRED KIDNEY FUNCTION AT THE TIME OF THE PROCEDURE, ABOUT A QUARTER IMPROVE, ABOUT A HALF ARE UNCHANGED, AND ABOUT 20 PERCENT GET WORSE, SO ON BALANCE IT'S A WASH. KIDNEY FUNCTION DOESN'T CHANGE FOR THE GROUP AS A WHOLE. SOME PATIENTS DEFINITELY IMPROVE, BUT THE NUMBER THAT IMPROVE ARE NOT REALLY MUCH GREATER THAN THE NUMBER THAT ARE SERIOUSLY HARMED BY THE INTERVENTION. AND IN THE RANDOMIZED CONTROLLED TRIALS, MOST HAVE SHOWN NO SIGNIFICANT DIFFERENCE IN KIDNEY FUNCTION OVER RELATIVELY SHORT PERIODS OF FOLLOW-UP, IN THIS CASE ONLY ABOUT 12 MONTHS IN THE DRASTIC TRIAL, WHICH YOU'VE HEARD ABOUT.

SO THERE'S NOT MUCH EVIDENCE THAT THIS IS GOING TO IMPROVE KIDNEY FUNCTION. AND WHY IS THAT? WELL, IT'S NOT SURPRISING FOR A COUPLE OF REASONS. FIRST OF ALL, PROSPECTIVE DATA LOOKING AT THE NATURAL HISTORY OF THESE RENAL ARTERY LESIONS SHOW THAT ACTUALLY IT'S A MINORITY OF THEM THAT PROGRESS TO COMPLETE OCCLUSION OVER A REASONABLY LONG PERIOD OF FOLLOW-UP OF SEVERAL YEARS. AND IN THIS LARGE SERIES FROM THE GROUP IN SEATTLE, ONLY ABOUT THREE PERCENT OF THE RENOVASCULAR LESIONS WENT ON TO COMPLETE OCCLUSION AND, THEREFORE, WOULD BE POSSIBLY A CAUSE

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OF END-STAGE RENAL DISEASE.
AND THEN LOOKED AT ANOTHER WAY, THERE'S A VERY POOR CORRELATION BETWEEN THE DEGREE OF ANATOMIC STENOSIS AND KIDNEY FUNCTION, AGAIN SUGGESTING THAT IT'S NOT THE MAIN RENAL ARTERY DISEASE PER SE THAT'S CAUSING RENAL DYSFUNCTION, AND HERE'S A COUPLE OF DIFFERENT DATA SETS THAT LOOK AT THIS. SO THIS IS THE CREATININE CLEARANCE RATE MEASURED IN A GROUP OF PATIENTS WITH DIFFERENT DEGREES OF RENOVASCULAR DISEASE RANGING FROM LESS THAN A 50 PERCENT STENOSIS OF A SINGLE ARTERY UP TO HIGH GRADE BILATERAL STENOSIS, AND YOU CAN SEE ALL OF THESE PATIENTS HAVE IMPAIRED KIDNEY FUNCTION WITH AN AVERAGE CREATININE CLEARANCE BETWEEN 30 AND 40, BUT THERE IS NO DIFFERENCE AT ALL BETWEEN THE DIFFERENT GROUPS.
AND THIS IS A STUDY LOOKING ISOTOPICALLY AT GFR IN PATIENTS WITH UNILATERAL STENOSIS IN THE KIDNEY DISTAL TO THE STENOSIS VERSUS GFR IN THE KIDNEY WITH THE NORMAL RENAL ARTERY, AND WHAT YOU CAN SEE IS THAT OFTEN THE GFR IN THE KIDNEY WITH THE NORMAL RENAL ARTERY IS AS LOW OR EVEN LOWER THAN THE GFR IN THE KIDNEY THAT'S DISTAL TO THE STENOSIS, AGAIN SUGGESTING THAT THE MAJOR CAUSE OF RENAL DYSFUNCTION IN THESE PATIENTS IS NOT THE RENAL ARTERY LESION BUT INTRINSIC KIDNEY DISEASE, AND THEREFORE

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UNLIKELY TO BE BENEFITED BY REVASCULARIZATION.
THERE'S REALLY NOTHING TO SAY ABOUT HEART FAILURE. THERE ARE NO RANDOMIZED CONTROLLED TRIALS. OBSERVATIONAL STUDIES SUGGEST THAT SOME PATIENTS DO BETTER AFTER STENTING, BUT OBVIOUSLY PATIENTS DO BETTER WITH INTENSIVE MEDICAL THERAPY ALSO.
SO IT'S FAIR TO SAY THAT MOST OF THESE TRIALS ARE SERIOUSLY FLAWED. THEY TEND TO LOOK AT SURROGATE ENDPOINTS LIKE BLOOD PRESSURE AND CREATININE RATHER THAN HARD CLINICAL OUTCOMES LIKE SURVIVAL OR CARDIOVASCULAR EVENTS. MANY EMPLOYED A VERY IMPRECISE DEFINITION OF RENAL ARTERY STENOSIS, ENROLLING PATIENTS WITH ONLY A 50 PERCENT STENOSIS OR GREATER. WHEN WE DO THIS IN CORAL, WE FIND THAT THESE ARE OFTEN OVER-READ, SO IF YOU SHOOT FOR A 50 PERCENT STENOSIS, ABOUT A QUARTER OF THE PATIENTS END UP HAVING LESS THAN THAT.
MANY OF THE STUDIES WERE SEVERELY HAMPERED BY LARGE NUMBERS OF CROSSOVERS, AND THEN I THINK ALMOST NONE OF THEM PAID ADEQUATE ATTENTION TO THE MEDICAL THERAPY THAT PATIENTS ARE RECEIVING, AND OBVIOUSLY COMPARING AN INTERVENTION TO AN INADEQUATE MEDICAL INTERVENTION IS A BIASED APPROACH.
SO WHAT IS OPTIMAL MEDICAL THERAPY IN RENAL ARTERY STENOSIS? THIS HAS ALREADY BEEN

DISCUSSED A LITTLE BIT. IT INCLUDES TIGHT CONTROL OF BLOOD PRESSURE DOWN TO, THESE ARE JUST JNC-7 TARGETS. THIS REQUIRES MULTIPLE DRUGS, AND IN THE CORAL STUDY AT LEAST, WE FELT THAT BLOCKADE OF THE RENIN/ANGIOTENSIN/ALDOSTERONE SYSTEM MAY BE CRITICAL. WE FEEL THAT THIS MAY BE ONE OF THE BAD ACTORS IN PATIENTS WITH RENAL ARTERY STENOSIS. IT'S IMPORTANT TO NOTE THAT IN MANY OF THE STUDIES THAT HAVE BEEN TALKED ABOUT, THESE DRUGS WERE SPECIFICALLY AVOIDED BECAUSE OF CONCERN THAT THEY COULD PRODUCE ACUTE RENAL FAILURE. THAT IS A REAL RISK, BUT IN FACT THE INCIDENCE OF SEVERE ACUTE RENAL FAILURE IN PATIENTS WITH RENOVASCULAR DISEASE TREATED WITH THESE DRUGS IS RELATIVELY LOW, AND IT IS POSSIBLE TO USE THESE AGENTS IN THE MAJORITY OF PATIENTS WITH RENOVASCULAR DISEASE. THAT MAY BE CRITICALLY IMPORTANT TO IMPROVING LONG-TERM OUTCOMES AND THERE IS SOME OBSERVATIONAL DATA THAT SUGGESTS THAT THAT IS TRUE. THESE ARE THE OTHER CONCOMITANT THERAPIES THAT SHOULD BE APPLIED. TREATING DYSLIPIDEMIA, SMOKING CESSATION, SOME KIND OF ANTIPLATELET THERAPY. BECAUSE MANY OF THESE PATIENTS ARE DIABETIC, GLYCEMIC CONTROL. AND THEN ALSO BECAUSE OF THE CHRONIC KIDNEY DISEASE, MANAGEMENT OF THE CONSEQUENCES OF THAT. AND IT'S DIFFICULT TO PREDICT WHAT THE

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EXACT OUTCOME OF THAT TYPE OF APPROACH WILL BE. AS YOU'VE ALREADY HEARD, THERE REALLY AREN'T GOOD PROSPECTIVE TRIALS LOOKING AT THE IMPACT OF AN INTENSIVE MEDICAL REGIMEN LIKE THAT ON CLINICAL OUTCOMES IN PATIENTS WITH RENOVASCULAR DISEASE, BUT BY EXTRAPOLATION FROM OTHER POPULATIONS YOU CAN MAKE SOME PREDICTIONS.

AND SO, THIS IS A STUDY OR REALLY A REVIEW THAT WAS PUBLISHED A FEW YEARS AGO IN LANCET WHICH PREDICTED THE CUMULATIVE RISK REDUCTION OF USING FOUR RELATIVELY SIMPLE MEDICAL INTERVENTIONS. SO ASPIRIN, BETA BLOCKERS, LIPID LOWERING AND ACE INHIBITORS, THERE'S RELATIVE RISK REDUCTIONS FROM EACH OF THESE.

AND AGAIN, THIS IS NOT FROM A RENAL ARTERY STENOSIS POPULATION, BUT IT'S FROM OTHER POPULATIONS WITH HYPERTENSION AND OTHER TYPES OF COMORBIDITIES. AND WHAT THIS PREDICTS IS ABOUT A 75 PERCENT CUMULATIVE RISK REDUCTION IN A HYPERTENSIVE POPULATION IF THESE THERAPIES ARE PROVIDED, AND IF YOU ADD SMOKING CESSATION, IT EVEN GETS A LITTLE BETTER.

AND I THINK THIS IS ANOTHER ONE OF THE PROBLEMS FOR INTERVENTIONS. SO EVEN IF IT'S A GOOD THERAPY AND EVEN IF IT REDUCES CLINICAL EVENT RATES IN THE PATIENTS WITH RENAL ARTERY STENOSIS, AS MEDICAL THERAPY HAS GOTTEN BETTER AND AS WE HAVE NOW

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EFFECTIVE WAYS OF CONTROLLING BLOOD PRESSURE, CONTROLLING LIPIDS AND TREATING THIS VERY AGGRESSIVELY, THAT WE'RE GOING TO BE REDUCING EVENT RATES IN THESE PATIENTS WHEN WE TREAT THEM WITH THIS TYPE OF REGIMEN, AND IT JUST BECOMES HARDER AND HARDER FOR THE INTERVENTIONS TO DO BETTER.

JUST TO MAKE THIS POINT, THIS IS AGAIN, ACTUALLY WE'RE RELYING ON STEVE TEXTOR HERE, WHO'S PUBLISHED A LOT, AND THIS IS JUST SOME LONG-TERM OUTCOMES DATA THAT HIS GROUP HAS PUBLISHED FROM THE MAYO CLINIC LOOKING AT PATIENTS TREATED WITHOUT REVASCULARIZATION. SO THESE ARE PATIENTS WITH RENAL ARTERY STENOSIS FOLLOWED FOR A NUMBER OF YEARS WITHOUT REVASCULARIZATION, AND WHAT YOU CAN SEE IS THAT IN FACT YOU CAN ACHIEVE GOOD BLOOD PRESSURE CONTROL. ALMOST HALF OF THE PATIENTS HAD BLOOD PRESSURE TREATED TO THE JNC TARGET OF LESS THAN 140 OVER 90, THE CREATININE REMAINS RELATIVELY STABLE OVER TIME, RELATIVELY FEW OF THESE PATIENTS NEED TO BE REVASCULARIZED, END-STAGE RENAL DISEASE IS VERY UNCOMMON.

AND MORTALITY IS SIGNIFICANT, BUT REMEMBER, WE'RE DEALING WITH AN ELDERLY POPULATION WITH A LOT OF COMORBIDITIES AND THIS MAY NOT REALLY BE THAT DIFFERENT IN AN ANGIOPLASTY OR STENT-TREATED

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GROUP.
SO JUST TO WRAP UP, RENAL ARTERY STENOSIS IS A COMMON PROBLEM THAT IS RELATIVELY EASY TO FIND. THE BEST TREATMENT, I FEEL, IS STILL UNKNOWN. THE PATIENTS ARE ILL. ALL PATIENTS REQUIRE AN INTENSIVE MULTIFACETED MEDICAL INTERVENTION. THE OUTCOMES FROM REVASCULARIZATION ARE UNPREDICTABLE. WE DON'T REALLY HAVE A WAY OF DECIDING UP FRONT WHICH PATIENTS WILL BENEFIT VERSUS WHICH WILL NOT, AND THE INTERVENTION DOES HAVE SOME RISKS.
A CLINICAL TRIAL IS NEEDED. THE CORAL TRIAL YOU'VE HEARD ABOUT A LITTLE BIT, HOPEFULLY WILL ADDRESS SOME OF THESE QUESTIONS AND, YOU KNOW, OUR ONLY CONCERN IS THAT ENROLLMENT IN THESE CLINICAL TRIALS BE ENCOURAGED. SO THAT IS ALL I HAVE TO SAY. THANK YOU.
DR. GARBER: THANK YOU, DR. DWORKIN. NEXT SPEAKING WILL BE DR. THOMAS SOS.
DR. SOS: GOOD MORNING. A LOT OF THIS IS BASED ON 34 YEARS OF EXPERIENCE IN BEING INVOLVED IN RENAL ARTERY, AND PARTLY UNDER THE TUTELAGE, EARLY TUTELAGE OF JOHN LOWER AND HIS GROUP. A LOT OF THIS WAS SUMMARIZED IN A PAPER IN ENDOVASCULAR TODAY ENTITLED RENAL STENTING TO DATE, IS THIS PROCEDURE UNDERUSED OR OVERUSED? YES. SO WHAT I WOULD LIKE TO

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DO IS SPEND THE REST OF THE HALF HOUR EXPLAINING TO YOU WHAT I MEANT BY THAT.
FIRST OF ALL, THE REAL QUESTION IS WHETHER STENTING IN RENAL ARTERY DISEASE IS JUSTIFIED TO PREVENT ISCHEMIC NEPHROPATHY AND RENOVASCULAR HYPERTENSION AND TO INCREASE LIFE EXPECTANCY AND PERHAPS REDUCE COMPLICATIONS. AND THE ANSWER IS YES AND NO, SO IF I COULD GO THROUGH THAT, WHEN SHOULD WE INTERVENE AND WHEN SHOULDN'T WE, WHAT DO WE KNOW OR AT LEAST WHAT DO WE THINK WE KNOW?
WE ALL KNOW THAT RENAL ARTERY STENOSIS, HYPERTENSION AND RENAL INSUFFICIENCY ARE RELATED AND THAT RENOVASCULAR HYPERTENSION, HYPERTENSIVE NEPHROPATHY AND ISCHEMIC NEPHROPATHY ARE THE CONSEQUENCES AND WHEN THEY ALL OCCUR TOGETHER, WE CAN HAVE RENOVASCULAR HYPERTENSION AND ISCHEMIC NEPHROPATHY.
SO, HOW DO WE DECIDE WHO WE SHOULD TREAT?
WELL, YOU CAN OBVIOUSLY LOOK AT THE BENEFIT, THE RISK, AND COMPARE IT TO THE NATURAL HISTORY. AND WHAT I WOULD LIKE TO IS SORT OF SORT OUT ALL THESE THINGS AND SEE WHICH FACTORS AFFECT THEM.
FIRST OF ALL, ONE OF THE ACCEPTED CRITERIA FOR INTERVENTION, AND I'M GOING TO TRY TO GO THROUGH THE CLINICAL, ANATOMIC AND PHYSIOLOGIC CRITERIA AND

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TRY TO PUT THEM INTO THIS BALANCE OF RISK, BENEFIT AND NATURAL HISTORY, AT LEAST WHAT WE THINK WE KNOW ABOUT IT.

WE KNOW THE CLINICAL CHARACTERISTICS OF RENOVASCULAR HYPERTENSION AND WE KNOW THAT BASICALLY THE END RESULT, END ORGAN DAMAGE IS GREATER WITH RENOVASCULAR HYPERTENSION THAN WITH CORRESPONDING LEVELS OF ESSENTIAL HYPERTENSION, AND WE ALL KNOW THE RISK FACTORS. FOR ISCHEMIC NEPHROPATHY, WE THINK WE KNOW THE CLINICAL CHARACTERISTICS, AND THAT IS NO INTRINSIC FRANK RENAL DISEASE, RECENT ONSET AND PROGRESSIVE AZOTEMIA, HYPERTENSION, OTHER VASCULAR DISEASE, SMOKING, AND USUALLY UNEQUAL KIDNEY SIZE, REPRESENTING THE UNEQUAL INVOLVEMENT OF THE TWO RENAL ARTERIES.

SO WHEN SHOULD WE INTERVENE? WELL, GENERALLY SPEAKING, IN RENAL DYSFUNCTION WHICH IS RECENT IN ONSET OR PROGRESSIVE, AND IS MODERATE OR SEVERE. IN HYPERTENSION WHICH IS SEVERE OR DIFFICULT TO CONTROL. IN PULMONARY EDEMA WHICH IS RECURRENT FLASH EDEMA. AND PERHAPS IN JEOPARDIZED RENAL PARENCHYMA, AND I'LL EXPLAIN THAT IN A FEW MOMENTS.

WHAT ARE THE CONTRAINDICATIONS CLINICALLY? WHILE ALL THESE WERE LISTED AT ONE TIME, I THINK THAT MOST OF THEM ARE NOT.

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NOW WHAT IS THE BEST ANATOMIC SCREENING?
WELL, YOU CAN GO THROUGH MRA, DUPLEX ULTRASOUND, CTA, INTRA-ARTERY DIGITAL, AND THESE ARE THE ANATOMIC CRITERIA THAT MOST OF US ACCEPT. CERTAINLY A SEVERE STENOSIS RESULTING IN AN 85 PERCENT CROSS-SECTIONAL AREA STENOSIS, ANGIOGRAPHIC POST-STENOTIC DILATATION, COLLATERALS, AND REDUCTION OF RENAL SIZE BEYOND THE EXPECTED VARIATIONS, THAT IS A LENGTH DISCREPANCY AT LEAST 1.5 CENTIMETERS AND A DOCUMENTED DIMINUTION IN LENGTH OF AT LEAST ONE CENTIMETER.
ARE THESE ANATOMIC CONTRAINDICATIONS TO THE INTERVENTION? WELL, AT ONE TIME THEY WERE THOUGHT TO BE. MOST OF US AGREE THAT THEY ARE NOT.
I THINK THE MOST IMPORTANT IS PHYSIOLOGIC SCREENING AND THE CRITERIA WE APPLY TO THEM.
RADIONUCLIDE SCANNING IS CURRENTLY EASY BUT UNFORTUNATELY UNRELIABLE IN BILATERAL DISEASE AND IN THE PRESENCE OF SERUM CREATININE. RENAL RENIN ASSAY IS ALSO AN ATTRACTIVE PHYSIOLOGICAL TEST, BUT AGAIN, IT'S UNRELIABLE IN BILATERAL DISEASE AND THE PRESENCE OF INCREASED SERUM CREATININE, AND IT IS INVASIVE.
DUPLEX ULTRASOUND IS UNFORTUNATELY TECHNICALLY DIFFICULT AND OPERATOR-DEPENDENT, BUT EVERY SINGLE PATIENT WHO UNDERGOES RENAL ANGIOPLASTY OR STENT COULD POTENTIALLY, AND I BELIEVE MORE THAN

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POTENTIALLY, SHOULD HAVE A MEASUREMENT OF THE AORTA RENAL PRESSURE GRADIENT AND SHOULD HAVE A MINIMUM OF A 10 PERCENT PEAK SYSTOLIC PRESSURE GRADIENT TO JUSTIFY INTERVENTION. NOW, I USED TO TALK ABOUT THE 10 PERCENT GRADIENT WITHOUT ANY GOOD DATA WHEN PEOPLE WERE TALKING ABOUT ABSOLUTE GRADIENTS OF 10 AND 15, AND SOMETIMES 20-MILLIMETER GRADIENT. INTERESTINGLY, DEBRUYNE DID A VERY NICE STUDY THAT DEMONSTRATED IN HUMANS AFTER STENTING AND PRODUCING GRADIENT STENOSIS, THAT GRADIENT READINGS DID NOT BEGIN UNTIL YOU REACHED A 10 PERCENT DROPOFF, A 10 PERCENT CHANGE, AND THEN YOU COULD SEE THAT GRADIENT READINGS BEGAN FROM THE STENOTIC KIDNEY AND ELEVATED, WERE SLIGHTLY ELEVATED SYSTEMICALLY.

SO I THINK THAT THIS STUDY SHOWS, AT LEAST IN TERMS OF RENIN PRODUCTION, WHICH MOST OF US AGREE IS A MARKER FOR THE MEASURE, THE BEST WAY TO EVALUATE AT LEAST EXPERIMENTALLY IS IN THE PRESENCE OF A SIGNIFICANT RENAL ARTERY STENOSIS. SO THAT I THINK ILLUSTRATES THAT A 10 PERCENT GRADIENT IS CERTAINLY THE MINIMUM JUSTIFIABLE.

PRACTICALLY, HOW DO WE MEASURE THIS? WE SHOULD HAVE A CATHETER WHICH IS SMALLER THAN FOUR FRENCH IN THE RENAL ARTERY AND MINIMALLY TO THE STENOSIS, A SHEATH LARGE ENOUGH IN THE AORTA OR THE

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FEMORAL ARTERY TO MEASURE THE AORTIC PRESSURE, AND IF THERE'S NO GRADIENT, IT MEANS EITHER THAT THE STENOSIS IS NOT PHYSIOLOGICALLY SIGNIFICANT OR THAT THERE'S AN INCREASED RENAL PERIPHERAL VASCULAR RESISTANCE, THE EQUIVALENT OF THE RESISTIVE INDEX BEING INCREASED, AND IN THESE CASES THERE SHOULD BE NO INTERVENTION BECAUSE THE KIDNEY IS NONSALVAGEABLE, OR SHOULDN'T BE.

SO WHAT IS OUR ALGORITHM? WE BELIEVE THAT CLINICAL SUSPICION AND PLASMA RENIN ACTIVITY WITH ACE INHIBITION, THE SO-CALLED CAPITAL CHALLENGE TEST, IS CERTAINLY A PRETTY GOOD OFFICE TEST TO SCREEN PATIENTS, AND THEN WE HAVE AVAILABLE ALL THESE TESTS. THE IMPORTANT THING IS TO TAKE ONE, THE ONE YOU REALLY DO BEST. I BELIEVE MRA WITH GADOLINIUM IS STILL, IN SPITE OF ALL THE SCARE WITH THE FIBROTIC, WHATEVER IT'S CALLED, LESIONS, IT'S PROBABLY ONLY IN 150 PATIENTS REPORTED WORLDWIDE AND IT SHOULDN'T SCARE PEOPLE AWAY FROM GADOLINIUM IN APPROPRIATE PATIENTS. AND IF YOU HAVE A STENOSIS WHICH LOOKS SIGNIFICANT, YOU SHOULD DO A DIGITAL THAT MEASURES THE PRESSURE AND, IF APPROPRIATE, INTUBATE OR TAKE THE PATIENT TO MEDICAL THERAPY.

AN ISCHEMIC NEPHROPATHY IS EVEN EASIER.

IF THE PATIENT DOES NOT HAVE KNOWN MEDICAL

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PARENCHYMAL DISEASE, YOU DO AN ULTRASOUND OR AN MRA LOOKING FOR RENAL SIZE ASYMMETRY, RENAL ARTERY STENOSIS, PERHAPS INCREASED RESISTIVE INDEX, BUT I DON'T BELIEVE THAT SHOULD DEPRIVE ANYONE OF INTERVENTION. MEASURE THE GRADIENT AND DO A DIGITAL. IF APPROPRIATE, INTERVENE, OR SEND THE PATIENT TO MEDICAL THERAPY. AND QUITE HONESTLY, TWO-THIRDS OF OUR PATIENTS AT CORNELL NOW FALL INTO THE ISCHEMIC NEPHROPATHY GROUP, NOT IN THE HYPERTENSION GROUP, BECAUSE THE HYPERTENSION GROUP IS SO HETEROGENEOUS AND THE ENDPOINT OF HYPERTENSION WITH CHANGING DRUG REGIMENS IN BETWEEN IS VIRTUALLY USELESS IN MY OPINION.

SO WHEN SHOULD YOU NOT INTERVENE? WELL, WHEN THERE IS NO SIGNIFICANT GRADIENT, WHEN THE BLOOD PRESSURE IS EASILY CONTROLLED, WHEN THERE'S MILD STABLE RENAL DYSFUNCTION. AND CERTAINLY IN INCIDENTALLY DISCOVERED STENOSIS WITHOUT PRIOR CLINICAL EVALUATION, YOU SHOULD NOT INTERVENE.

SO OBVIOUSLY WHAT I'D LIKE TO DO IS TO SORT OF GO THROUGH NOW WHAT I BELIEVE IS SOME OF THE JUSTIFICATION OR LACK OF JUSTIFICATION IN THE LITERATURE. CERTAINLY YOU WANT TO INTERVENE WHEN THE BENEFIT IS GREATER THAN THE RISK, AND THEY EXCEED THAT OF THE NATURAL HISTORY OF THE DISEASE.

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SO LET'S TALK A LITTLE BIT ABOUT THE NATURAL HISTORY. I THINK THE BEST STUDY, THE PROSPECTIVE STUDY BY CAPS THAT I ALREADY ALLUDED TO, AND THEY BASICALLY SHOWED THAT ALTHOUGH RENAL ARTERY STENOSIS IS PROGRESSIVE, PROGRESSION TO OCCLUSION IS VERY RARE. AND THESE ARE SOME OF THE DATA AND IT SHOWS THAT THE HIGHER THE STENOSIS AT THE BEGINNING, THE GREATER THE PROGRESSION. IT ALSO SHOWED THAT 60 PERCENT STENOSIS PROGRESSED GREATER THAN NORMAL. AND IT SHOWED THAT PROGRESSION OF OCCLUSION IS VERY INFREQUENT AND RARE, AS YOU ALREADY HEARD.

NOW ONE DAY I JUST LOOKED AT THE U.S. CENSUS DATA AND I MUST SAY THAT WAS QUITE A WHILE AGO, SO THIS DATA IS NOT PROPORTIONATELY ACCURATE, BUT THIS IS WHEN THERE WERE 78 MILLION PEOPLE IN THE U.S. POPULATION OLDER THAN 50, AND WHAT I DID WAS I LOOKED AT THE DATA IN THE LITERATURE FOR THE PREVALENCE OF THE DISEASE AND THE PROGRESSION OF THE DISEASE, AND I APPLIED THAT TO THE U.S. POPULATION, AND THESE ARE THE DATA. AND IT CAME OUT THAT ABOUT 8.5 MILLION PATIENTS SHOULD BE PROGRESSING TOWARD RENAL DYSFUNCTION, BUT WE KNOW FROM MY OWN DATA THAT IT'S AROUND 11,000. NOW YOU CAN ALTER EACH OF THESE BY A FACTOR OF SEVERAL, BUT IT'S STILL VALID.

THIS IS THE SAME FOR PATIENTS OLDER THAN

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74 AND IT'S SIMILAR DATA.
SO, I BELIEVE THAT THE PREVALENCE AND
PROGRESSION OF RENAL ARTERY STENOSIS AND RENAL
DYSFUNCTION ARE EXAGGERATED. ALMOST ALL PROGRESSION
DATA PREDATE CURRENT SMOKING CESSATION, DIET,
EFFECTIVE BLOOD PRESSURE AND GLUCOSE CONTROL, AND
STATINS. AND NO LARGE RETROSPECTIVE -- OR NO LARGE
PROSPECTIVE RANDOMIZED STUDY HAS EVER BEEN DONE TO
COMPARE MEDICAL THERAPY, SURGERY OR STENTING, CORAL
HOPEFULLY BEING THE EXCEPTION.
ALL RIGHT. SO LET ME LOOK AT A WHOLE
BUNCH OF DIFFERENT POTENTIAL TREATMENTS. ONE OF THE
REAL MAJOR ISSUES, I BELIEVE, THAT CONFRONTS ALL OF
US, IS WHAT DO WE DO WITH CLINICALLY AND
PHYSIOLOGICALLY NONSIGNIFICANT RENAL ARTERY STENOSIS?
IN OTHER WORDS, DOES PROPHYLACTIC RENAL ARTERY
STENTING WORK, WHAT'S THE EVIDENCE FOR IT?
WELL, A LOT OF THE EVIDENCE IS BASED ON
THE FACT THAT RENAL ARTERY STENOSIS MAY BE AN
INDEPENDENT VARIABLE IN LIFE EXPECTANCY. AND SOME OF
THE DATA CITED TO SUPPORT THIS IS THIS STUDY FROM
SCOTLAND WITH 121 CONSECUTIVE PATIENTS WHO HAD RENAL
ARTERY STENOSIS AND HYPERTENSION. THE QUESTION IS,
AND I SUSPECT RENAL ARTERIAL HYPERTENSION, WHICH IS
DIFFERENT THAN RENAL ARTERY STENOSIS. AND THEY

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SHOWED THAT THE FIVE TO 12-YEAR SURVIVAL WAS LOWER THAN IN AGE AND SEX-MATCHED HYPERTENSIVE CONTROLS WHO DID NOT HAVE RENAL ARTERY STENOSIS.

THE PROBLEM WITH THIS IS THAT RENAL ARTERY STENOSIS IS NOT RENAL ARTERY HYPERTENSION, AND RENAL ARTERY STENOSIS IS ALSO A MARKER FOR GENERALIZED VASCULAR DISEASE INCLUDING CORONARY AND CEREBROVASCULAR, WHICH DO AFFECT LIFE EXPECTANCY. IN FACT, THESE AUTHORS THEMSELVES SAID THAT MULTIVARIATE ANALYSIS SHOWED THAT AGE, CIGARETTE SMOKING AND PRESENCE OF ATHEROMATOUS DISEASE WERE SIGNIFICANTLY AND INDEPENDENTLY RELATED TO OUTCOMES AMONG THE PATIENTS WITH RENOVASCULAR DISEASE.

THE SECOND PAPER THAT'S CITED BY ADVOCATES OF SO-CALLED PROPHYLACTIC STENTING IS A PAPER BY ZELLER, WHO SHOWED THAT EVENT-FREE SURVIVAL AFTER RENAL ARTERY STENTING WAS SIGNIFICANT. BUT AN ANALYSIS OF THE SUBSET SHOWED THAT WHEN YOU HAD RELATIVELY LOW SERUM CREATININE TO START, PERHAPS THAT IS NORMAL, VERSUS IN BETWEEN AND VERY SEVERE ELEVATION OF SERUM CREATININE, SHOWED PROGRESSIVELY DIMINISHED SURVIVAL. THIS IS KIND OF INTUITIVE AND WE ALL KNOW THAT. HOWEVER, HE WENT ON TO CONCLUDE THAT SURVIVAL AFTER SUCCESSFUL STENTING FOR SEVERE RENAL ARTERY STENOSIS DEPENDS ON BASELINE SERUM

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CREATININE AND LEFT VENTRICULAR FUNCTION, AND EFFORTS MUST BE MADE TO AVOID THE DEVELOPMENT OF ADVANCED ISCHEMIC NEPHROPATHY AND CONGESTIVE HEART FAILURE, AND APPLE PIE SHOULD BE HANDED OUT FREELY. WE ALL AGREE.

HE WENT ON, HOWEVER, TO SAY THESE DATA EMPHASIZE THE NEED FOR CORRECT AND EARLY DIAGNOSIS OF RENAL ARTERY STENOSIS AND THE NEED TO TREAT THESE PATIENTS AS EARLY AS POSSIBLE TO PREVENT THE DEVELOPMENT OF RENAL FAILURE, WITH A REDUCED LIFE EXPECTANCY. THE TROUBLE IS THAT BY TREATMENT, HE MEANT STENT THESE PATIENTS AS EARLY AS POSSIBLE.

NOW, THESE DATA DO PROVE THE NEED FOR CORRECT AND EARLY DIAGNOSIS OF THE RENAL ARTERY STENOSIS, BUT THEY DO NOT PROVE THE NEED TO STENT CLINICALLY AND PHYSIOLOGICALLY NONSIGNIFICANT STENOSES AS EARLY AS POSSIBLE. THEY PROBABLY DO PROVE THE NEED TO MEDICALLY TREAT THESE PATIENTS WITH STATINS, ET CETERA, TO PREVENT THE DEVELOPMENT OF RENAL INSUFFICIENCY, ET CETERA.

NOW THE ADVOCATES OF PROPHYLACTIC AND EARLY STENTING SAY THAT IF YOU INTERVENE EARLY, YOU WILL BE WORKING IN A CLEANER AORTA, IT WILL BE A TECHNICALLY EASIER PROCEDURE WITH HIGHER SUCCESS, FEWER COMPLICATIONS, AND YOU MAY BE ABLE TO ALTER THE

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CLINICAL COURSE OF THE PATIENT. AGAINST THIS IS THE FACT THAT THERE IS NO LONG-TERM BENEFIT PROVEN, AND THERE CAN BE NO IMMEDIATE BENEFIT IN SOMEBODY WHO IS NOT AS SYMPTOMATIC NOR HAS SIGNIFICANT DISEASE. CURRENT MODERN MEDICAL THERAPY MAY BE EQUALLY EFFECTIVE AND THE COMPLICATIONS MAY LEAD TO DIALYSIS, EITHER EARLY OR LATE WHEN THEY BECOME MORE SIGNIFICANT.

NOW MEDICAL THERAPY, THE GOALS ARE PREVENTION, SLOWING PROGRESSION, ALTERING THE CLINICAL COURSE, JUST AS IN INTERVENTIONS, AND THE METHODS ARE OBVIOUSLY GLYCEMIC CONTROL, LIPID CONTROL, ANTIHYPERTENSIVES, ALTERED LIFESTYLE, AND I GUESS PLATELET INHIBITION AS YOU ALREADY HEARD, AND WE DON'T KNOW HOW EFFECTIVE THAT IS EITHER.

SO IF YOU DECIDE, HOWEVER, NOT TO INTERVENE FOR A PHYSIOLOGICALLY NONSIGNIFICANT STENOSIS, BUT YOU KNOW THAT THE STENOSIS EXISTS, YOU ARE OBLIGATED TO HAVE AGGRESSIVE LIPID, GLUCOSE AND LIFESTYLE MODIFICATIONS, FOLLOW THE PATIENT'S BLOOD PRESSURE, SERUM CREATININE, RENAL SIZE, PERCENT STENOSIS EVERY THREE TO SIX MONTHS. AND IF SERUM CREATININE GOES UP OR THE BLOOD PRESSURE BECOMES UNCONTROLLED OR THE KIDNEY SIZE DIMINISHES, THEN I THINK YOU ARE JUSTIFIED IN INTERVENING. BY THE WAY,

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THESE ARE PROBABLY VERY MUCH THE SAME THAT YOU WOULD DO IN A PATIENT WHO DID HAVE INTERVENTIONS. NOW LET'S LOOK AT THE JUSTIFICATION FOR MEDICAL THERAPY FOR CLINICALLY AND PHYSIOLOGICALLY NONSIGNIFICANT RENAL ARTERY STENOSIS. WELL, WE KNOW FROM THIS META-ANALYSIS OF TEN STUDIES IN THE CAROTID ARTERIES THAT FOR ATHEROSCLEROSIS, WE KNOW THAT STATINS ARE EFFICIENT AND SAFE TO DECREASE THE RATE OF CAROTID ATHEROSCLEROSIS IN THE LONG TERM, AND AGGRESSIVE STATINS MAY EVEN PROVIDE SUPERIOR EFFICACY FOR CAROTID ATHEROSCLEROSIS REGRESSION. WE ALSO KNOW THE CORONARY BENEFIT, THE INFLUENCE OF ALTERING THE LDL AND HDL LEVELS, AND THIS STUDY SHOWS VERY NICELY THAT AS THERE IS REDUCTION OF LDL OR HDL, CORONARY PLAQUE REGRESSES, AND THIS IS THE PLAQUE VOLUME REGRESSING, AND HERE IS THE LEVEL, THE HDL, AND THE CHANGES IN PLAQUE LEVEL AGAIN GOING BEYOND INTO REGRESSION, AND YOU CAN SEE THAT IN BOTH OF THESE PLAQUE REGRESSIONS. YOU CAN ALSO LOOK AT ANOTHER STUDY ON INTENSIVE VERSUS MODERATE LIPID LOWERING, WHICH IS A FAIRLY CLASSIC STUDY NOW ON ACUTE CORONARY SYNDROMES, AND YOU CAN SEE THAT GIVING A MORE AGGRESSIVE LEVEL OF PRAVASTATIN RESULTS IN DIMINUTION OF THE MACE THAT DEFINITELY LEADS TO A MAJOR CARDIOVASCULAR EVENT.

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AND HERE YOU CAN SEE THAT EVEN IN A RELATIVELY SHORT PERIOD OF TIME, OUT TO A YEAR AND A HALF, WE CAN BEGIN TO SEE, AND TO TWO YEARS, WE CAN BEGIN TO SEE A SIGNIFICANT REDUCTION OF MACE IN THESE PATIENTS.
HERE'S ANOTHER PEER STUDY LOOKING AT THE LEVEL OF STATIN THERAPY AND AGAIN, YOU CAN SEE THAT WITH CONTROLS OF LDL LEVELS, THE PROGRESSION OF ATHERORENAL DISEASE BECOMES SIGNIFICANTLY BELOW, OR AT LEAST EVEN BELOW BASELINE, AND IN CRP IT'S EVEN MORE SIGNIFICANT.
SO, A VERY RECENT PAPER ON FACTORS AFFECTING LONG-TERM SURVIVAL FOLLOWING RENAL ARTERY STENTING CONCLUDED THAT PATIENTS RECEIVING LIPID-LOWERING TREATMENT HAD A REDUCTION IN MORTALITY COMPARED TO THESE NOT BEING TREATED. THESE RESULTS MAY REPRESENT PLAQUE STABILIZATION OR DELAYED PROGRESSION OF ATHEROSCLEROTIC CORONARY ARTERY DISEASE. IT MAY ALSO REPRESENT AN EFFECT ON RENAL ARTERY STENOSIS PROGRESSION AND POSSIBLY PRESERVATION OF RENAL FUNCTION LEADING TO AN OVERALL LOWER MORTALITY.
NOW, THIS IS THE FIRST STUDY THAT EVEN HINTED SPECIFICALLY ABOUT THE BENEFIT FOR RENAL ARTERY DISEASE WITH LIPID REDUCTION. AND INTERESTINGLY, ZELLER COMMENTED ON THIS, AND HE SAID

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THE BENEFICIAL OUTCOME OF THIS STATIN DRUG THERAPY FOR PATIENTS WITH RENAL ARTERY STENOSIS CONFIRMS THE STUDY RESULTS OF SECONDARY PREVENTION WITH STATINS IN PATIENTS WITH CAD AND CAROTID ARTERY DISEASE.

OKAY. SO LET'S LOOK AT THE RISKS OF INTERVENTION. WHILE WE ALL KNOW THAT CHOLESTEROL EMBOLIZATION IS PROBABLY THE FIRST AND FOREMOST, THERE ARE ALL KINDS OF MECHANICAL PROBLEMS IN CONTRAST NEPHROPATHY, AND WITH STENT EMPLOYMENT ALL KINDS OF TECHNICAL ISSUES. BUT CHOLESTEROL EMBOLIZATION IS PROBABLY THE CRITICAL ISSUE WHICH HAS BEEN REPORTED IN TWO OR THREE PERCENT, BUT VERY FEW STENT SERIES HAVE MANY PATIENTS WITH AZOTEMIA, THAT IS PATIENTS WHO WILL SHOW THAT CHOLESTEROL EMBOLIZATION HAS GLOBALLY CLINICALLY OCCURRED. AND IN SPITE OF THAT, MOST STENT SERIES REPORT A 25 PERCENT DETERIORATION OF RENAL FUNCTION, WHICH IS OFTEN ASCRIBED TO NATURAL HISTORY, CONTRAST NEPHROTOXICITY, BUT CHOLESTEROL EMBOLIZATION AT LEAST USED TO BE VERY RARELY LOOKED FOR, EVEN THOUGH MANY OF US SCREAMED ABOUT IT FOR MANY YEARS.

NOW, I THINK THIS IS PROBABLY THE BEST WAY TO BEGIN TO UNDERSTAND THIS. THIS IS THE GFR CURVE, AND YOU CAN SEE THAT I COULD TAKE OUT ONE OF YOUR KIDNEYS OR CHOLESTEROL EMBOLIZING TOTALLY, AND IN

TERMS OF GLOBAL RENAL FUNCTION MEASURED BY SERUM CREATININE, YOU WOULD NEVER KNOW THE DIFFERENCE, YOUR SERUM RENAL FUNCTION WOULD BE NORMAL. AND IT REALLY ISN'T UNTIL YOU REACH THE KNEE OF THIS EXPONENTIAL CURVE WHERE EVEN 10 PERCENT ADDITIONAL LOSS OF RENAL PARENCHYMA WILL PUT YOU FROM MARGINAL RENAL FUNCTION ON TO DIALYSIS.

SO IF YOU ARE MUCKING AROUND WITH PATIENTS IN THE GREEN ZONE, YOU CAN STILL CHOLESTEROL-EMBOLIZE THEM AND NO ONE, INCLUDING YOU AND THE PATIENT, WILL BE WISER. IF YOU ARE TREATING PATIENTS WHERE THE PATIENT POPULATION IS MORE SENSITIVE, THEN YOU WILL FIND MORE CHOLESTEROL EMBOLI.

SO, THAT SORT OF LEADS ME TO AN ANALYSIS OF EMBOLIC PROTECTION AND, LET'S SEE, HOW DO WE DECIDE WHETHER IT WORKS. WELL, WHAT'S THE PROBLEM, WHAT ARE THE SOLUTIONS, THE QUALITY AND QUANTITY OF EVIDENCE, ARE THERE CONFOUNDING VARIABLES, AND PERHAPS OTHER SOLUTIONS. SO WE KNOW THAT CHOLESTEROL EMBOLIZATION MANIFESTS WITH DETERIORATION OF RENAL FUNCTION, LIVEDO RETICULARIS, ABDOMINAL PAIN THAT CAN BUILD IN THE GI TRACT, AND PERIPHERAL EOSINOPHILIA. AND I'VE ALREADY SHOWN THAT IT IS RELATIVELY RARELY REPORTED, AND PERHAPS WE WILL FIND OUT FROM CORAL WHAT THE ANSWER IS.

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LET ME JUST SHOW YOU A TYPICAL PATIENT WITH A LOVELY AORTA AS YOU SEE HERE, SEVERE RENAL ARTERY STENOSIS BILATERALLY, AND YOU CAN SEE WHAT THE PROBLEM IS. HERE IS THE RENAL ARTERY OSTIUM SURROUNDED BY ALL THIS HORRENDOUS ATHEROSCLEROMA, AND YOU KNOW THAT JUST SCRAPING A DIAGNOSTIC CATHETER BY THIS, NEVER MIND TRYING TO PUT A PROTECTION DEVICE OR A GUIDE WIRE ACROSS IT, IS GOING TO SCRAPE OFF CHOLESTEROL PARTICLES AND EMBOLIZE THEM. IN THIS PARTICULAR PATIENT, BECAUSE THE OTHER KIDNEY WAS NOT AS SEVERELY INVOLVED, WE DID INTERVENE AND SUCCESSFULLY PLACED A STENT, AND THIS PATIENT ACTUALLY GOT A SLIGHT BIT BETTER.

HERE IS AN EXAMPLE OF WHAT HAPPENS. THIS IS CERTAINLY NOT AMENABLE TO A PROTECTION DEVICE. THIS CHOLESTEROL EMBOLIZATION OCCURRED ONE WEEK AFTER A SUCCESSFUL INTERVENTION WHEN THE CREATININE INITIALLY RESPONDED, AND A WEEK LATER BUMPED, AND WE KNOW THAT ONCE YOU STIR UP CHOLESTEROL IN THE AORTIC WALL, IT MAY CONTINUE TO EMBOLIZE EVEN WITHOUT FURTHER INTERVENTION.

NOW, THERE WAS A VERY INTERESTING EX VIVO STUDY WHERE THEY TOOK A CHUNK OF THE AORTAL ARTERY AND DID TYPICAL MANIPULATIONS INVOLVED, AND THEY MEASURED THE SIZE AND NUMBER OF PARTICLES. THE

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MANIPULATIONS INVOLVED PUTTING GUIDE WIRES ACROSS, BALLOONS AND STENTS, ET CETERA. BUT SIGNIFICANTLY, IF YOU LOOK AT THE PATIENTS WHO HAVE PARTICLES OF SMALLER THAN 10 MICRONS AND PARTICLES THAT ARE HALF A MILLIMETER TO A MILLIMETER, YOU WILL NOTICE THAT SMALLER THAN 10 MICRON WERE THREE MILLION, AND LARGER THAN HALF A MILLIMETER WERE FOUR. SO THE REAL PROBLEM IS THE VERY TINY CHOLESTEROL EMBOLI, AND THE FILTERS HAVE A FILTER PORE SIZE OF 100 MICRONS. CLEARLY THEY ARE NOT GOING TO FILTER THESE PARTICLES. THE QUALITY OF EVIDENCE IS EVEN WORSE. THIS IS A PAPER BY HENRY, 2005, WHO SAID THAT DESPITE GOOD IMMEDIATE AND LONG-TERM RESULTS, POST-PROCEDURAL DETERIORATION OF RENAL FUNCTION IS A CONCERN. IN 20 TO 40 PERCENT OF PATIENTS, ATHEROEMBOLISM IS A BIG DEAL. THE SAME DR. HENRY IN 2003 SHOWED THAT IN 56 PATIENTS, 18 HAD RENAL INSUFFICIENCY. HE USED A PROTECTION DEVICE AND SHOWED THAT MOST OF THE PATIENTS WERE STABLE, A FEW IMPROVED, AND NONE GOT WORSE. THAT SOUNDS TERRIFIC. IN 2001 THE SAME DR. HENRY SHOWED THAT IN 28 PATIENTS, 12 WITH RENAL INSUFFICIENCY, HE GOT SIMILARLY GREAT RESULTS WITH PROTECTION. TERRIFIC. THERE'S ONLY ONE PROBLEM. IN 1999 WITHOUT

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PROTECTION DEVICES, THE SAME DR. HENRY SHOWED 210 PATIENTS, OF WHOM 48 HAD RENAL INSUFFICIENCY. AND 29 PERCENT IMPROVED, 67 PERCENT WERE STABLE, AND ONLY TWO PATIENTS OR FOUR PERCENT GOT WORSE. SO THIS IS STATISTICALLY TOTALLY INVALID. THIS MUCH LARGER SHOWS THE SAME RESULTS AS PROTECTION WHEN HE USED IT. HERE'S ANOTHER -- HOW MUCH TIME DO I HAVE LEFT?

DR. GARBER: YOU HAVE ABOUT THREE MINUTES.

DR. SOS: OKAY. I'VE GOT TO SPEED UP.

THIS IS ANOTHER STUDY ABOUT PROTECTION BY HOLDEN IN 2003, WHERE HE BASICALLY COMPARED HIS RESULTS WITHOUT PROTECTION AND WITH PROTECTION, AND IT SHOWED MARKEDLY IMPROVED RESULTS WITH PROTECTION, VERY FEW ADVERSE EVENTS AS COMPARED TO WITHOUT, BUT THE NUMBERS WERE SMALL. THE ONLY PROBLEM WAS THAT HIS TECHNIQUE INVOLVED GETTING ACROSS WITH A SMALL CATHETER, USING THE APPROPRIATE DRUGS, USING A VERY SMALL GUIDE WIRE, AND THEN JAMMING AN EIGHT FRENCH OR ALMOST THREE-MILLIMETER DIAMETER DEVICE THROUGH BEFORE HE DEPLOYED THE FILTER. SO I THINK THAT THIS WAS A SHAM PROTECTION DEVICE AND IT'S SORT OF LIKE GOING OUT IN THE RAIN AND WALKING AROUND LIKE THIS, AND THEN WHEN YOU GET HOME YOU PUT UP YOUR UMBRELLA. IN 2006 HE ACTUALLY DID HAVE BETTER RESULTS WITH A

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BETTER TECHNIQUE AND THESE ARE PROBABLY, DEPENDING ON WHETHER YOU TRUST HIM AFTER ALL THAT, SHOWED IMPROVEMENT.

THERE'S ANOTHER STUDY BY EDWARDS, 26 PATIENTS, AGAIN A VERY SMALL STUDY, WHICH SHOWED THAT VERY FEW PATIENTS GOT WORSE AFTER USING PROTECTION.

SO THERE ARE MANY, MANY PROBLEMS WITH THE PROTECTION DEVICE. THERE ARE TECHNICAL ISSUES, THERE ARE ISSUES OF THE SIZE OF THE PORES, THERE ARE ISSUES THAT CHOLESTEROL EMBOLIZATION MAY OCCUR BEFORE YOU DEPLOY YOUR PROTECTION DEVICE, AND THEY MAY NOT WORK BECAUSE THE PORE SIZE IS TOO BIG, OR THERE MAY BE ISCHEMIA, OR JUST EMPLOYING THE DEVICE MAY BE A REAL ISSUE. SO MICROCHOLESTEROL EMBOLIZATION IS A PROBLEM, THERE MAY BE OTHER WAYS TO DEAL WITH IT, BUT CERTAINLY WE SHOULD DEAL WITH IT, AND CORAL MAY GIVE US THE ANSWER.

SO IN SUMMARY, IS STENTING IN CLINICALLY AND PHYSIOLOGICALLY SIGNIFICANT RENAL ARTERY STENOSIS JUSTIFIED TO PREVENT OR REVERSE ISCHEMIC NEPHROPATHY AND RENOVASCULAR HYPERTENSION, AND THE ANSWER TO THAT IS YES.

PALMAZ ONCE SAID ONCE THE DIAGNOSIS OF RENAL ARTERY STENOSIS IS ESTABLISHED, PARTICULARLY IN PATIENTS WITH DECREASED RENAL FUNCTIONAL RESERVE,

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RENAL ARTERY STENOSIS SHOULD BE TREATED WITHOUT DELAY. TO THAT I ADDED HEMODYNAMICALLY SIGNIFICANT RENAL ARTERY STENOSIS.

SO THE BENEFITS: THE DRASTIC STUDY REPORTEDLY SHOWED THAT THERE WAS NO BENEFIT. IN FACT, YOU'LL SEE THE RANDOMIZATION. 22 WENT TO ANGIOPLASTY OR THE MEDICAL GROUP, AND I THINK ACTUALLY INSTEAD OF BEING THE CASE AGAINST, THE RESULTS SHOWED FEWER DRUGS, MEDICAL GROUP WAS WORSE, SO ACTUALLY IT PROVES THE CASE FOR INTERVENTION.

I'M JUST GOING TO RUSH PAST ALL THIS IF I COULD. WHAT I WANT TO SHOW YOU, IF I CAN GET THIS THING TO MOVE, THE PROBLEM WITH ALL THESE STUDIES IS THAT THE OUTCOME CRITERIA, THE PATIENT SELECTION AND QUANTITATIVE, QUALITATIVE, THEY DON'T ALL REPORT THE SAME DATA AND THEY'RE SORT OF COMPARING PEARS AND APPLES.

AND THIS IS FOR RECURRENT PULMONARY EDEMA.

NOW, THIS IS THE RENAL FUNCTIONAL RESULT WITHOUT PROTECTION, AND YOU CAN SEE PRETTY MUCH OVERALL THE SAME DATA THAT WE'VE BEEN HEARING, 28 PERCENT IMPROVED, 44 PERCENT STABLE, 28 PERCENT WORSE. AND AGAIN THE QUESTION IS -- OOPS, CAN I GO BACK? HOW DO I GO BACK ONE SLIDE? OKAY, GREAT.

SO, IS CORAL THE ANSWER? WELL, THE

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INITIAL PROTOCOL RANDOMIZED AFTER THE AORTOGRAM IN MANY PATIENTS WITH MODERATE LESIONS, GRADIENTS OR PAIN, AND IN THE OTHERS A VISUAL ESTIMATE WHICH WE ALL KNOW IS PRETTY INACCURATE WHEN USED, AND THE PROTECTION DEVICE INITIALLY WAS PRETTY CRUDE. THE PROTOCOL WAS REVISED AND NOW RANDOMIZES NONINVASIVELY, WHICH I BELIEVE IS A BIG ADVANTAGE, AND THE USE AND PROTECTION DEVICE IS ALSO OPTIONAL, WHICH I ALSO THINK IS BIG ADVANTAGE.

SO THERE IS NO EVIDENCE-BASED CLINICAL DATA TO SUPPORT PROPHYLACTIC ANGIOPLASTY AND STENTING. THE LONG-TERM DURABILITY OF STENTS IS NOT KNOWN. EFFECTIVE LIPID CONTROL MAY BE JUST AS GOOD. THEREFORE, PROPHYLACTIC STENTING IS NOT JUSTIFIED. AND THAT'S WHAT THIS SLIDE SAYS, NO PROPHYLACTIC STENTING OF NONSIGNIFICANT LESIONS. ON THE OTHER HAND, SMELL THE STATINS. IT'S THE STATINS, STUPID, THE NEW PARADIGM.

IS STENTING IN RENAL ARTERY STENOSIS JUSTIFIED TO PREVENT ISCHEMIC NEPHROPATHY AND MACE?

YES.

SO PROPHYLACTIC STENTING IS NOT JUSTIFIED.

IN CLINICAL AND PHYSIOLOGICAL RENAL ARTERY STENOSIS, INTERVENTION WITH STENTS IS JUSTIFIED. THANK YOU VERY MUCH.

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DR. GARBER: THANK YOU, DR. SOS. NEXT, DR. LINAS, AND I'M GOING TO ASK YOU TO BE VERY STRICT IN STICKING WITH YOUR TIME HERE.

DR. LINAS: THANK YOU VERY MUCH FOR INVITING ME TO SPEAK. MY NAME IS STU LINAS, I'M FROM THE UNIVERSITY OF COLORADO HEALTH SCIENCES CENTER. THE ONLY DISCLOSURE I HAVE, I'M ON THE DSSB OF THE CORAL STUDY.

I WAS ASKED TO SPEAK REGARDING A PAPER PUBLISHED IN THE AMERICAN JOURNAL OF NEPHROLOGY EARLIER THIS YEAR AUTHORED BY A NUMBER OF INDIVIDUALS, ONE OF WHICH YOU'VE HEARD MENTIONED SEVERAL TIMES ALREADY TODAY, AND OUR TITLE WAS CONTROVERSIES IN RENAL ARTERY STENOSIS: A REVIEW BY THE AMERICAN SOCIETY OF NEPHROLOGY ADVISORY GROUP ON HYPERTENSION.

THIS IS WHAT I WOULD LIKE TO ACCOMPLISH TODAY. AFTER A BRIEF OVERVIEW I'M GOING TO TRY TO DEAL WITH THE FOLLOWING QUESTIONS: DO WE KNOW THE PREVALENCE OF RENAL ARTERY STENOSIS, AND MOST IMPORTANTLY, ISCHEMIC NEPHROPATHY? WHAT ARE THE RISKS ASSOCIATED WITH RENAL ARTERY STENOSIS? WHAT IS THE NATURAL HISTORY OF RENAL ARTERY STENOSIS? WHAT IS THE BEST TEST TO DIAGNOSE RENAL ARTERY STENOSIS AND ISCHEMIC NEPHROPATHY. AND FINALLY, WHAT ARE THE

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RESULTS WITH BLOOD PRESSURE AND CKD OF CURRENT THERAPIES?

RENAL ARTERY STENOSIS CAN BE OF TWO VARIETIES, IT CAN CAUSE RENOVASCULAR HYPERTENSION OR ISCHEMIC NEPHROPATHY. AT LEAST FOR -- THE DATA I WANT TO SHOW YOU TODAY, WE'RE TALKING ABOUT INDIVIDUALS OVER THE AGE OF 40, AND ALL THESE PATIENTS HAVE ATHEROSCLEROSIS.

NOW THE DEFINITION OF ISCHEMIC NEPHROPATHY THAT WE USE WAS PROPOSED BY DR. TEXTOR A COUPLE YEARS AGO, DEFINED AS IMPAIRMENT OF RENAL FUNCTION BEYOND OCCLUSIVE DISEASE OF THE MAIN RENAL ARTERY. YOU'LL SEE WHY THAT'S IMPORTANT IN JUST A LITTLE BIT.

SO WHAT IS THE PREVALENCE OF RENAL ARTERY STENOSIS VERSUS ISCHEMIC NEPHROPATHY? WELL, IF YOU DO A BROAD BRUSH STROKE OF ATHEROSCLEROTIC RENAL ARTERY STENOSIS, THE PREVALENCE OF A 50 PERCENT OR GREATER NARROWING OF THE RENAL ARTERY IS ALL OVER THE PLACE, OVERALL SOMEWHERE BETWEEN 11 AND 40 PERCENT. THIS IS THE VARIATION DURING AUTOPSY, UNDER AGE 60, OVER AGE 60, IN THE PRESENCE OF CORONARY STENOSIS, IN THE ABSENCE, TRIPLE VASCULAR DISEASE, ET CETERA, ET CETERA. IT REALLY IS ALL OVER THE PLACE. AND IN TRYING TO GET A HANDLE ON THAT, IT LOOKS LIKE IT DEPENDS ON THE POPULATIONS YOU LOOK AT.

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SO THIS IS A STUDY THAT DR. LEVIN DID A COUPLE YEARS AGO LOOKING AT THE PREVALENCE OF RENAL ARTERY STENOSIS IN PATIENTS UNDERGOING CARDIAC CATHETERIZATION WHO WERE CONSIDERED AT RISK FOR THE DISEASE. THE RISK FACTORS ARE THE USUAL PLAYERS, SEVERE HYPERTENSION, UNEXPLAINED CKD, PULMONARY EDEMA WITH HYPERTENSION, SEVERE ATHEROSCLEROSIS, EITHER CAROTID OR PERIPHERAL VASCULAR. AND SO WHAT THESE INVESTIGATORS FOUND IN A GROUP OF ABOUT 840 PATIENTS, 40 PERCENT OF THE TOTAL GROUP HAD 50 PERCENT RENAL ARTERY STENOSIS. ABOUT 14 PERCENT HAD 50 PERCENT LESION OR MORE, SEVEN PERCENT A 70 PERCENT LESION OR MORE. IT OCCURRED IN PATIENTS WITH SEVERE ATHEROSCLEROSIS; THIS WAS A MUCH SMALLER NUMBER THAN I WOULD HAVE EXPECTED. 16 PERCENT WITH RENAL DYSFUNCTION, NINE PERCENT OF HYPERTENSIVES, ET CETERA, ET CETERA.
WHEN ONE DID MULTIVARIATE ASSOCIATIONS, THE BIGGEST ASSOCIATION IN THIS STUDY WAS THE PRESENCE OF CAROTID DISEASE, PERIPHERAL VASCULAR DISEASE. INTERESTING, AND THOUGH NOT REPORTED IN OTHER STUDIES, MORE IN WOMEN, AGE, ET CETERA, ET CETERA. AND SO AT LEAST IN THIS POPULATION, A 40 PERCENT PREVALENCE WITH PERIPHERAL VASCULAR DISEASE.
NOW LOOK AT THIS POPULATION. VERY

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DIFFERENT THAN ALLUDED TO BEFORE. THIS IS THE PREVALENCE OF RENOVASCULAR DISEASE IN THE ELDERLY, A POPULATION-BASED STUDY. THIS WAS A CARDIOVASCULAR HEALTH STUDY, MULTICENTER, LONGITUDINAL COHORT STUDY IN FORSYTH COUNTY, NORTH CAROLINA, AND DUPLEX WAS USED TO DETERMINE THE INCIDENCE, AND HERE IT IS. THE OVERALL INCIDENCE IN THIS FREE LIVING POPULATION WAS ABOUT SEVEN PERCENT, VERSUS THE 40 PERCENT IN THE HIGH RISK POPULATION. THIS IS THE AGE INFORMATION, THIS ONE MORE MALE THAN FEMALE.
KIND OF THE SAME ACROSS RACE. WE DON'T HAVE TIME TO DISCUSS IT TODAY, THIS HAS BEEN CONTROVERSIAL, BUT IT'S SAID TO OCCUR FEWER TIMES IN AFRICAN-AMERICANS. PROBABLY NOT SO BASED ON THIS AND OTHER DATA. SO THAT'S RENAL ARTERY STENOSIS, MUCH MORE IMPORTANT FOR US TODAY.
WHAT ABOUT RENAL ARTERY STENOSIS AS A CAUSE OF END-STAGE RENAL DISEASE? AND IT REALLY DEPENDS ON THE CRITERIA USED TO MAKE THE DIAGNOSIS OF RENAL ARTERY STENOSIS. IS IT DOPPLER DUPLEX DATA, IS IT AORTOGRAM, PATHOLOGY, OR MOST IMPORTANTLY, IS IT THE DEFAULT DIAGNOSIS IN THE CORRECT CLINICAL SETTING? AND WHEN YOU LOOK AT THIS DATA, YOU COME TO THE CONCLUSION THAT IT'S SOMEWHERE BETWEEN FIVE AND EIGHT PERCENT OF THOSE WITH END-STAGE RENAL DISEASE.

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THIS IS A RECENT STUDY THAT SHOWS THE PROPORTION OF PATIENTS WITH RENOVASCULAR DISEASE LISTED AS THE PRIMARY CAUSE OF END-STAGE RENAL DISEASE FROM THE USRDS DATA SYSTEM. YOU'VE GOT A HANDOUT, UNFORTUNATELY I MISLABELED IT. THE UPPER LINE IS CORRECT HERE, THIS IS THE DIAGNOSTIC CLAIMS DATA, AND YOU CAN SEE OVER THE LAST TEN YEARS THIS HAS INCREASED FROM ABOUT SEVEN PERCENT UP TO MAYBE 11 OR 12 PERCENT, BUT IF YOU LOOK AT THE MEDICAL EVIDENCE REPORTS OF THOSE COMING ON TO END-STAGE RENAL THERAPY, IT'S BEEN PRETTY ROCK STABLE AT SOMEWHERE BETWEEN FIVE AND SIX PERCENT. AND SO AT LEAST AS A CAUSE OF END-STAGE RENAL DISEASE, MAYBE IT'S BEEN PRETTY STABLE OVER THE LAST COUPLE OF DECADES.

SO WHAT ARE THE RISKS ASSOCIATED WITH RENAL ARTERY STENOSIS? YOU'VE HEARD A LOT OF THIS ALREADY. THIS DATA I'M GOING TO SHOW YOU IS ALSO MEDICARE CLAIMS DATA, A FIVE PERCENT SAMPLE THAT KALRA PUT TOGETHER. THESE ARE COMPARISONS TO THE GENERAL POPULATION FROM A COUPLE YEARS AGO AND THIS IS THE ADVERSE EVENT RATE PER THOUSAND PATIENT YEARS OF THOSE WITH RENAL ARTERY STENOSIS COMPARED TO A CONTROLLED POPULATION. ABOUT A THREEFOLD INCREASE IN ATHEROSCLEROTIC HEART DISEASE, ABOUT A THREEFOLD

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INCREASE IN STROKE OR TIA, THREEFOLD INCREASE IN PERIPHERAL VASCULAR DISEASE, HEART DISEASE, MOST IMPORTANT IN DEATH PER SE, AND IN THIS PARTICULAR STUDY A 29-FOLD INCREASE IN THE PRESENCE OF RENAL REPLACEMENT THERAPY.

YOU'VE HEARD THE DATA ABOUT RENAL ARTERY STENOSIS OVERALL SURVIVAL, YOU'VE SEEN THE DATA FROM CHRIS COOPER OF PLUS-MINUS RENAL ARTERY STENOSIS. THIS IS THE DATA ON SURVIVAL OF THOSE WITH LESIONS THAT ARE LESS THAN 75 PERCENT OF THE RENAL ARTERY AND LESIONS THAT ARE GREATER THAN 75 PERCENT OF THE RENAL ARTERY, AND THERE'S A NICE CORRELATION OF SURVIVAL HERE, IN THAT IF YOU HAVE THE DISEASE, OVER THE SEVEN OR EIGHT YEARS OF FOLLOW-UP, THIS IS A BAD ACTOR AS FAR AS SURVIVAL IS CONCERNED.

HOW ABOUT SURVIVAL AFTER DEVELOPING END-STAGE RENAL DISEASE, AND IT TURNS OUT THAT COMPARED TO OTHER TYPES OF CKD, THIS IS A BAD ACTOR. SO, THESE ARE INDIVIDUALS DYING IN THE FIRST YEAR, THIS IS USRDS DATA FROM 2006. ALL END-STAGE RENAL DISEASE IN THIS COUNTRY, ABOUT A BALLPARK, 22 PERCENT ONE-YEAR DEATH RATE. TYPE 2 DIABETES, ABOUT THE SAME. HYPERTENSION, YOU KNOW, A HAIR MORE. BUT THESE ARE INDIVIDUALS WITH RENAL ARTERY STENOSIS, ABOUT A 40 PERCENT DECREASE IN SURVIVAL, INCREASE IN

00100

DEATH RATE THE FIRST YEAR OF THOSE WHO HAVE RENAL ARTERY STENOSIS.
SO WHAT'S THE NATURAL HISTORY OF RENAL ARTERY STENOSIS? IF YOU HAVE IT, WHAT'S IT MEAN AS FAR AS THE PATIENT IS CONCERNED? WELL, IT REALLY DEPENDS ON WHAT YOU'RE LOOKING AT IT FOR, THE NATURAL HISTORY. ARE WE TALKING ABOUT RENAL ARTERY DIAMETER, ARE WE TALKING ABOUT GFR, OR, MOST IMPORTANTLY, ARE WE TALKING ABOUT RENAL ATROPHY?
AND SO THIS IS THE RENAL ARTERY DIAMETER DATA THAT WE PUT TOGETHER. WE FELT THAT IF ONE LOOKS AT PROGRESSION, SOMEWHERE BETWEEN 25 AND 75 PERCENT, AND I'LL COME BACK TO THAT. OCCLUSION, SOMEWHERE BETWEEN EIGHT AND 16 PERCENT. AND THE RESULTS REALLY DEPEND ON THE INITIAL EXTENT OF THE LESION; A TIGHT LESION IS WORSE FOR YOU THAN NOT SO TIGHT LESION. THE TIME OF FOLLOW-UP. MOST IMPORTANTLY, YOU'LL SEE, THE METHODS USED TO DETERMINE RENAL ARTERY STENOSIS AND THE INDICATIONS FOR THE ADDITIONAL STUDIES. WAS IT A CORONARY ARTERY DISEASE DRIVE-BY ARTERIOGRAM, WAS IT FOR PERIPHERAL VASCULAR DISEASE, OR WAS IT SPECIFICALLY FOR RENAL ARTERY STENOSIS.
AND SO HERE IS SOME OF THE CORONARY ARTERY ANGIOGRAM STUDY. THIS IS A SEVEN OR EIGHT-YEAR FOLLOW-UP OF INDIVIDUALS THAT HAD ANGIOGRAMS AND WERE

00101

FOLLOWED UP. YOU CAN SEE THAT WHETHER ONE HAD A 25 PERCENT LESION DURING THE FIRST ANGIOGRAM, THIS INCREASED FROM ABOUT FIVE TO 10 PERCENT; A 50 PERCENT LESION A BIT MORE; A 75 PERCENT LESION. BOTTOM LINE IS THAT OVER SEVEN OR EIGHT YEARS OF FOLLOW-UP, THE CORONARY DATA SAYS THAT IF YOU HAD IT INITIALLY, IT'S GOING TO PROGRESS OVER THE NEXT SEVEN OR EIGHT YEARS. THIS IS THE DATA FROM SEATTLE ON RENAL ARTERY DIAMETER BY DUPLEX SCAN IN PATIENTS WITH PERIPHERAL VASCULAR DISEASE. IT'S INTERESTING DATA. FIVE YEARS OF FOLLOW-UP. THESE ARE INDIVIDUALS WHO HAD NORMAL RENAL ARTERIES TO START WITH, LESS THAN 60 PERCENT LESIONS, GREATER THAN 60 PERCENT LESIONS. AND WHAT I WANT YOU TO SEE HERE IS THAT AT THE END OF FIVE YEARS, IF YOU HAD PERIPHERAL VASCULAR DISEASE TO START WITH, EVEN THOUGH YOU HAD A NORMAL VESSEL TO START WITH, AFTER FIVE YEARS, 20 PERCENT NOW HAD ABNORMAL LESIONS. IF YOU HAVE A LESS THAN 60 PERCENT LESION, THIS PROGRESSED DRAMATICALLY. IF YOU HAD MORE THAN A 60 PERCENT LESION, THIS PROGRESSED AS WELL. SO IF YOU HAVE CORONARY DISEASE, IT PROGRESSES, NOT SO BAD. IF YOU HAVE PERIPHERAL VASCULAR DISEASE, IT PROGRESSES AND IT LOOKS LIKE IT'S FAIRLY STRIKING.

AND SO, THIS IS THE RENAL ARTERY DATA.

00102

HOW ABOUT PROGRESSION AS ASSESSED BY GFR OR NEED FOR END-STAGE RENAL DISEASE THERAPY RATHER THAN RENAL ARTERY PATENCY, I.E., THE REAL DISEASE WE'RE TALKING ABOUT TODAY, ISCHEMIC NEPHROPATHY. WELL, IT TURNS OUT THAT IT AIN'T SO EASY TO PREDICT END-STAGE RENAL DISEASE PROGRESSION THAT'S BASED ON GFR OR RENAL ARTERY DIAMETERS WHEN ONE COMES INTO THE STUDY.

I'M GOING TO SHOW YOU A NUMBER OF STUDIES OVER THE LAST FOUR OR FIVE YEARS. FOR THE MOST PART THEY'RE SMALL, THEY'RE NOT LARGE, BUT THEY MAKE A POINT THAT I WANT TO MAKE WITH YOU. AND SO, THESE ARE INDIVIDUALS WITH GREATER THAN 50 PERCENT LESIONS, WHO ARE -- SORRY, THESE ARE CONTROLLED INDIVIDUALS. THESE ARE INDIVIDUALS WITH GREATER THAN 50 PERCENT LESIONS. AND WHAT I WANT YOU TO SEE HERE IS IF YOU LOOK AT SERUM CREATININE, CERTAINLY OVER THE FIRST SIX YEARS OF THIS STUDY, WHETHER YOU DID OR DIDN'T HAVE A 50 PERCENT LESION, IT DIDN'T LOOK LIKE THERE WAS MUCH PROGRESSION. BETWEEN SIX AND EIGHT YEARS, IT LOOKS LIKE THESE TWO GROUPS SEPARATED. IT WOULD BE NICE TO KNOW WHAT THEY LOOKED AT THEREAFTER, BUT WE DON'T HAVE THAT DATA.

IT TURNS OUT ALSO, AS YOU'VE HEARD ALREADY, PROXIMAL NARROWING DOES NOT PREDICT GFR EITHER AT THE BEGINNING OF THE STUDY OR THE

00103

FOLLOW-UP. AND SO HERE IS THE BEGINNING STUDY, THIS IS AN INDEX OF LUMEN PATENCY GREATER THAN 1.5, AND IN THESE INVESTIGATORS' STUDY WAS CONSIDERED LESS THAN A 25 PERCENT LESION, PROGRESSING DOWN TO LESS THAN 0.5 LUMEN PATENCY, THEIR MARKER. AND YOU CAN SEE, WHETHER YOU HAD LESS THAN A 25 PERCENT LESION OR MORE THAN ROUGHLY A 75 PERCENT LESION, OVER THE THREE TO FIVE YEARS OF THIS STUDY, THERE WAS NO LOSS OR CHANGE IN GFR OVER TIME.

THIS IS A VERY IMPORTANT STUDY, I THINK, WHEN YOU THINK ABOUT THIS DISEASE, BECAUSE IT REALLY GETS AT THE DIFFERENCE BETWEEN THE RENAL ARTERY PER SE AND THE DEGREE OF HIDDEN DISEASE AS WELL. THIS IS, TIME TO END-STAGE RENAL DISEASE IS NOT RELATED TO CONTRALATERAL RENAL ARTERY ANATOMY. AND THIS IS A STUDY THAT LOOKS AT INDIVIDUALS WHO COME IN WITH UNILATERAL RENAL ARTERY STENOSIS, TIGHT STENOSIS ON ONE SIDE. THE OTHER SIDE IS EITHER NORMAL, HAS SIGNIFICANT RENAL ARTERY STENOSIS, MORE THAN A 50 PERCENT LESION, INSIGNIFICANT RENAL ARTERY STENOSIS, OR RENAL ARTERY OCCLUSION.

AND SO IF YOU COME INTO THIS WITH ONE KIDNEY DOWN AND THE OTHER KIDNEY NORMAL, THEN THE ROUGHLY SIX OR SEVEN-YEAR FOLLOW-UP IS THAT YOUR DIALYSIS FREE SURVIVAL IS PRETTY GOOD. IT AIN'T

00104

PERFECT, BUT IT'S PRETTY GOOD. IN CONTRAST, IF YOU COME IN WITH ONE KIDNEY DOWN AND RENAL ARTERY OCCLUSION, THEN YOU DON'T DO VERY WELL OVER THE NEXT FIVE OR SIX YEARS.

IT'S THIS MIDDLE DATA THAT'S FASCINATING TO US, AND THAT IS THESE ARE INDIVIDUALS WITH LESS THAN A 50 PERCENT LESION. AND YOU CAN SEE, WITH LESS THAN A 50 PERCENT LESION, THEY DID WORSE THAN THOSE WITH A 50 PERCENT LESION. STATED DIFFERENTLY, IF ONE LOOKED AT AN ANALYSIS OF THE CONTRALATERAL ANATOMY, YOU'VE GOT A NORMAL KIDNEY, YOU SET THE RELATIVE RISK AT ONE; INSIGNIFICANT RENAL ARTERY STENOSIS, THE RISK WAS OVER THREE; SIGNIFICANT RENAL ARTERY STENOSIS, NOT A LOT DIFFERENT THAN NORMAL. SO AGAIN, THE RENAL ARTERY DIAMETER DOESN'T LOOK LIKE THE MAJOR PLAYER.

THESE ARE THE SAME INDIVIDUALS NOW, AND NOW WHAT WE'RE GOING TO LOOK AT IS THE GFR ON THE OTHER SIDE. THESE ARE INDIVIDUALS WITH A NORMAL GFR, THESE ARE INDIVIDUALS WHO HAD A GFR GREATER THAN 25 MLS PER MINUTE, AND REMEMBER, THIS IS A SOLITARY KIDNEY, THESE ARE INDIVIDUALS WITH GFR BETWEEN 10 AND 25, AND THESE ARE INDIVIDUALS WITH LOW GFR. AND YOU GET THE SENSE HERE THAT IN THIS PARTICULAR STUDY, THE ISSUE IS NOT RENAL ARTERY DIAMETER, BUT BASICALLY GFR THAT REALLY DETERMINES IT. AND SO HERE ARE THE

00105

RELATIVE RISKS. SET AT ONE; 1.41 IF THE GFR GOES TO 25 TO 50; 10 TO 25 A FOURFOLD INCREASE; IF IT WAS LESS THAN 10, A 30-FOLD INCREASE.

AND SO HERE'S THE ANATOMY DATA, THE GFR DATA. HOW ABOUT IF YOU LOOK AT THE RENAL BIOPSY SCORE IN INDIVIDUALS WITH RENAL ARTERY STENOSIS? A SMALL STUDY, THERE ARE A COUPLE OF THESE SMALL STUDIES, AND WHAT I WANT YOU TO SEE HERE IS OVER TIME IF YOU LOOK AT CHANGE IN CREATININE CLEARANCE AND SOME INDICATION OF RENAL DAMAGE OR FIBROSIS, NEPHROSCLEROSIS, ET CETERA, YOU CAN SEE THAT OVER THE TIME OF FOLLOW-UP, THAT IN FACT THERE WAS A TIME RELATIONSHIP BETWEEN WHAT THE BIOPSY LOOKS LIKE AND PROGRESSION. SO THE BEST PREDICTOR OF PROGRESSION IS CLEARLY NOT RENAL ARTERY DIAMETER; IT'S GFR UPON PRESENTATION AND/OR THE EXTENT OF RENAL FIBROSIS.

SO WHAT'S THE BEST TEST TO DIAGNOSE RENAL ARTERY STENOSIS OR ISCHEMIC NEPHROPATHY? YOU'VE HEARD THIS ALREADY. THERE ARE A WHOLE BUNCH OF TESTS OUT THERE, BE IT ACEI-INDUCED INCREASES IN RENIN, ACEI RENOGRAPHY, DUPLEX ULTRASOUND, MRAS, AND OF COURSE THERE ARE OTHER STUDIES AS WELL. THE BOTTOM LINE WHEN ONE LOOKS AT SENSITIVITY, SPECIFICITY OR POSITIVE PREDICTIVE VALUE, WHETHER YOU USE ACEI RENOGRAPHY, DUPLEX, MRA OR CAPTOPRIL RENOGRAM, IF YOU

00106

LOOK AT THIS DATA, IT'S ALL OVER THE PLACE AND ALL LOOKS THE SAME. AND SO JUST BECAUSE IT'S CLOSEST TO ME, THE POSITIVE PREDICTIVE VALUE CONSISTENTLY WAS SOMEWHERE BETWEEN 70 AND 100 PERCENT WHEN WE LOOKED AT THIS DATA.

AND SO HERE'S A PROBLEM WITH THE NONINVASIVES. ANOTHER TELLING STUDY, THIS IS AN INTERESTING STUDY BY THIS INVESTIGATOR, AND WHAT HE WAS LOOKING FOR IS, HE WAS LOOKING FOR A FOUR-POINT SCALE OF AGREEMENT, EITHER NOTHING, NO LESION, A LESS THAN 50 PERCENT LESION, GREATER THAN 50 PERCENT LESION, OR A GREATER THAN 80 PERCENT LESION AMONG SIX TO SEVEN RADIOLOGISTS. NOW I WOULD HAVE THOUGHT THAT THAT WOULD BE A NO-BRAINER, THAT THE RADIOLOGISTS COULD GET THEIR ACT TOGETHER ON THIS ONE.

HERE'S THE DATA. WITH DSA, ABOUT 40 PERCENT AGREEMENT. WITH MRA IT LOOKS LIKE ABOUT 60 PERCENT AGREEMENT, FLOW STUDY, ABOUT 40 TO 50 PERCENT AGREEMENT. SO HERE'S THE PROBLEM. IF THE RADIOLOGISTS CAN'T AGREE ON THIS STUFF, HOW THE REST OF US WHO ARE PRIMARY PROVIDERS ARE GOING TO AGREE, IT'S TOUGH. AND SO WHEN ONE LOOKS AT ATHEROSCLEROTIC RENAL ARTERY STENOSIS, THE BEST TEST REALLY IS CENTER DEPENDENT, THE LITERATURE IS FAR BETTER THAN REALITY, AND THE BOTTOM LINE, AT LEAST FOR US, IS THAT IF GFR

00107

IS OVER 50, ALL ARE ABOUT THE SAME; IF THE GFR IS UNDER 50, I DON'T THINK WE HAVE THAT DATA TO TAKE A STAND ON THE BEST TEST.

SO HERE'S THE CLINICAL DILEMMA. THE TESTS WHICH WERE USEFUL IN DIAGNOSING RENAL ARTERY STENOSIS ARE USEFUL IN DIAGNOSING RENAL ARTERY STENOSIS RATHER THAN ISCHEMIC NEPHROPATHY. ISCHEMIC NEPHROPATHY IS REALLY A PATHOLOGICAL DIAGNOSIS. ARE THERE ADEQUATE SURROGATES FOR PATHOLOGY? THE RENAL ULTRASOUND FOR SIZE AND DENSITY IS LIFE-CHANGER. THE RENAL DOPPLER DETERMINATION OF RESISTIVE INDEX HAS BEEN FORWARDED AS SOMETHING WE CAN UTILIZE, AND I'LL SHOW YOU WHAT WE FEEL ABOUT THAT IN JUST A LITTLE BIT.

SO WHAT ARE THE RESULTS FOR BLOOD PRESSURE AND PROGRESSION OF CKD FOR CURRENT THERAPY? DR. BALK HAS SHOWN YOU THE TECHNICAL ANALYSIS. I WOULD REMIND YOU THAT OVER THE LAST SEVERAL YEARS THE NUMBER, THE VOLUME HAS INCREASED FROM ABOUT 7,000 UP TO 18,000, AND THAT WAS THE YEAR 2000. MY SENSE IS IT PROBABLY HAS DOUBLED OR MORE SO SINCE THEN.

WHAT ARE THE BENCHMARKS THAT DEFINE SUCCESS? WE HAVE NOT BEEN VERY GOOD AT DEFINING THAT. ARE WE TALKING ABOUT DEATH OR ARE WE TALKING ABOUT RENAL OUTCOMES? AND IF WE'RE TALKING ABOUT RENAL OUTCOMES, IS IT RENAL ARTERY PATENCY, LOSS OF

00108

GFR, OR NEED FOR RENAL REPLACEMENT THERAPY? WHAT ARE THE CARDIOVASCULAR OUTCOMES, MI, STROKE, HEART FAILURE, COMBINED OUTCOMES, ET CETERA? SO THE CARDIOVASCULAR OUTCOMES, AS LANCE AND CHRIS COOPER SAID BEFORE, WE REALLY DON'T HAVE PROSPECTIVE STUDIES, WE'RE WAITING FOR THE CORAL STUDIES AS FAR AS THOSE OUTCOMES ARE CONCERNED.

HOW ABOUT BLOOD PRESSURE AND RENAL OUTCOMES? WELL, WHEN WE LOOKED AT THIS DATA, WE THOUGHT IN A SUMMARY OF THE NINE STUDIES WE LOOKED AT, THAT SOMEWHERE BETWEEN 15 AND 52 PERCENT IMPROVED RENAL FUNCTION, 28 TO 81 PERCENT WERE STABLE, AND MOST IMPORTANTLY, FOUR TO 54 PERCENT ACTUALLY WERE REPORTED TO HAVE GOTTEN WORSE AFTER STENT PLACEMENT. SO AS FAR AS STENT IS CONCERNED, OUR CONCLUSIONS WERE IT PROBABLY IMPROVED BLOOD PRESSURE. THERE ARE NO QUALITY COMPARATIVE TRIALS. COMPARED TO ANGIOPLASTY ALONE, IT DOES LOOK LIKE THERE'S LESS RESTENOSIS, BETTER PATENCY, BUT REMEMBER, THIS IS ONLY SIX-MONTH DATA.

NOW HOW ABOUT SURGERY? THIS HAS BEEN SHORT-SHRIFTED A LITTLE BIT TODAY AND I WANT TO SHOW YOU A RECENT STUDY TO GIVE YOU SOME SENSE OF WHERE I THINK WE ARE AS FAR AS SURGERY IS CONCERNED. THESE ARE INDIVIDUALS WITH PRE-OP SERUM CREATININE LESS

00109

THAN 1.8, 1.8 TO ABOUT THREE, AND ABOVE THREE. AND SO LOOK AT THIS WITH ME FOR A SECOND. IF YOUR CREATININE WAS LESS THAN 1.8, ABOUT 30 PERCENT GOT BETTER, 60 PERCENT NO CHANGE, AND STILL, SOME GOT WORSE. IF YOUR CREATININE WAS BETWEEN 1.8 AND THREE, ABOUT 54 PERCENT GOT BETTER IN THIS STUDY, ROUGHLY 40 PERCENT THE SAME, A FEW LESS GOT WORSE. AND THESE ARE INDIVIDUALS WITH CREATININE OF THREE, AND THE STUDY SHOWED THAT 58 PERCENT IMPROVED, 34 PERCENT HAD NO CHANGE, AND ABOUT EIGHT PERCENT GOT WORSE.

SO THE BOTTOM LINE IN THIS SURGICAL STUDY WAS, AGAIN, NO COMPARISONS, NOT RANDOMIZED, WAS THAT THE RESULTS MAY BE A LITTLE BIT BETTER THAN WE'VE HEARD AS FAR AS TODAY IS CONCERNED.

THIS IS DR. BALK'S SLIDE THAT YOU'VE SEEN ALREADY AS FAR AS THE RESULTS OF INTERVENTION. I DON'T WANT TO REPRODUCE THAT, I JUST WANT TO SAY IN OUR OBSERVATION OR IN OUR STUDY THAT WE PUT TOGETHER BEFORE THIS, WE CAME TO THE SAME CONCLUSIONS THAT DR. BALK DID.

SO WHY DOESN'T SUCCESSFUL REVASCULARIZATION IMPROVE RENAL FUNCTION? IF YOU'RE FIXING THE RENAL ARTERY, KIND OF, WHY DOESN'T THAT? AND THE REAL DEAL IS, AS DR. TEXTOR ALLUDED TO BEFORE, THAT IT REALLY IS DOWNSTREAM RENAL ATROPHY,

00110

DOWNSTREAM RENAL FIBROSIS THAT'S THE NAME OF THE GAME. SO HOW DO YOU ASSESS IT? YOU CAN ASSESS IT BY KIDNEY SIZE AND ECHOGENICITY, KIND OF VERY, VERY SOFT LIGHT CHANGERS. YOU CAN ASSESS IT BY RENAL BIOPSY, PRETTY INVASIVE, YOU CAN'T BE DOING THAT IN MOST PATIENTS. IT'S BEEN SAID TO BE ASSESSABLE BY MRA; THERE'S A LOT OF ISSUES NOW WITH MRA IN THOSE WITH ESTIMATED GFRS LESS THAN 60. AND THE NEW PLAYER OVER THE LAST SEVERAL YEARS HAS BEEN THE DUPLEX DOPPLER RESISTIVE INDEX.

THIS IS THE RADERMACHER STUDY THAT ALL OF YOU ARE FAMILIAR WITH AND HAVE SEEN. THIS IS THAT RESISTIVE INDEX PREDICTED CHANGE IN GFR AFTER REVASCULARIZATION. THESE ARE INDIVIDUALS WITH LOW RESISTIVE INDICES WHO HAD NO CHANGE IN GFR AFTER REVASCULARIZATION. THESE ARE INDIVIDUALS WITH HIGH RESISTIVE INDICES WHO DID POORLY AFTER REVASCULARIZATION. THIS HAS BEEN KIND OF THE GOLD STANDARD THAT MANY OF US WERE LOOKING FOR.

REPRODUCTION, WHEN THEY DID UNIVARIATE ODDS RATIOS, WHEN THE RESISTIVE INDEX IS HIGH IT WAS VERY HELPFUL. NO RESPONSE TO ACEI RENOGRAPHY, A LITTLE LESS HELPFUL. LOWER GFR, PROTEIN EXCRETION, ET CETERA, ET CETERA. THIS REALLY LOOKED TO BE VERY PREDICTIVE AND VERY HELPFUL TO US, BUT IT TURNS OUT

00111

IT AIN'T QUITE AS CLEAN AS WE HAVE BEEN LED TO BELIEVE.
NOW THIS IS A RELATIVELY SMALL STUDY BUT I THINK A VERY IMPORTANT STUDY, THAT SAYS RESISTIVE INDEX DOES NOT PREDICT CHANGES IN GFR AFTER REVASCULARIZATION. THIS IS A STUDY THAT LOOKED AT SERUM CREATININE BEFORE AND SHORTLY AFTER REVASCULARIZATION. SO IT AIN'T PERFECT, BUT IT GIVES YOU SOME SENSE THAT MAYBE IT'S NOT GREAT. THESE ARE INDIVIDUALS WITH LOW RESISTIVE INDICES; THIS IS THE CREATININE BEFORE AND AFTER REVASCULARIZATION, NO PROBLEM. THESE ARE RESISTIVE INDICES BETWEEN .7 AND .8 THAT, YOU CAN SEE THAT ON AVERAGE, EVEN THOUGH THE RESISTIVE INDEX WAS HIGH, SOME OF THESE INDIVIDUALS GOT BETTER. THESE ARE INDIVIDUALS WITH VERY HIGH RESISTIVE INDICES AND YOU CAN SEE THAT A NUMBER OF THESE INDIVIDUALS GOT BETTER AFTER REVASCULARIZATION. SO EVEN THE RESISTIVE INDEX THAT WE ALL THOUGHT WAS GOING TO BE HELPFUL HAS SOME PROBLEMS.
SO, WHICH PATIENTS WITH RENAL ARTERY STENOSIS SHOULD BE STENTED, OR MAYBE OFFERED SURGERY? AND SO AT LEAST FROM OUR PERCEPTION, NOT EVERYONE WITH RENAL ARTERY STENOSIS. IF WE'RE DOING IT FOR CARDIOVASCULAR PROTECTION, WE'RE AWAITING THE RESULTS

00112

OF THE CORAL STUDY. AT LEAST FOR RENAL PROTECTION WHEN WE LOOK AT THIS DATA, WE THINK THAT THE PEOPLE WHO ARE MOST LIKELY TO BENEFIT ARE THOSE WITH A RECENT INCREASE IN CREATININE AND THOSE WITH A LOW RESISTIVE INDEX. AND SO AT LEAST FROM THE RENAL SIDE OF IT, THIS WOULD BE THE TARGET ORGAN, TARGET GROUP WE WOULD BE SHOOTING AT, AND FOR CARDIOVASCULAR PROTECTION, WE'RE EAGERLY AWAITING THE RESULTS OF THE CORAL STUDY AS WELL. THANK YOU VERY MUCH.

DR. GARBER: THANK YOU, DR. LINAS. WE NOW HAVE A SET OF SCHEDULED SPEAKERS AND THE FIRST SPEAKER WILL BE DR. CHRISTOPHER WHITE.

DR. WHITE: THANK YOU VERY MUCH. IT'S A PLEASURE TO BE HERE. I REPRESENT THE SOCIETY OF CARDIAC ANGIOGRAPHY INTERVENTIONS, THEY PAID FOR MY TRAVEL HERE TODAY. OTHER THAN THAT, I HAVE NO FINANCIAL CONFLICTS RELATED TO THIS TOPIC.

I WOULD LIKE TO ADDRESS THE ISSUE OF CORRELATION OF RENAL FUNCTION, AND THIS IS THE THIRD DISPLAY, AS I'VE BEEN COUNTING, OF DR. TEXTOR'S DATA. AND AGAIN, TO ME, THIS DATA SUGGESTS THAT THERE ARE SIGNIFICANT PROBLEMS WITH THE NATURAL HISTORY OF RENAL ARTERY DISEASE, AND CLEARLY FOR BILATERAL OR SOLITARY RENAL ARTERY DISEASE.

AGAIN, THE THIRD OR FOURTH REPRESENTATION

00113

OF DR. CAPS' DATA. CLEARLY THE MORE SIGNIFICANT THE DISEASE, THE MORE LIKELIHOOD OF THE CHANCE OF RENAL ATROPHY. RENAL ATROPHY IS CLEARLY A SURROGATE, BUT I THINK A VERY EFFECTIVE SURROGATE FOR THE LOSS OF RENAL FUNCTION. SO THE MORE LIKELY THE PROGRESSION, THE MORE SEVERE THE STENOSIS, THE MORE LIKELY ATROPHY.

AND THEN FINALLY, DEMONSTRATION THAT IF PATIENTS PROGRESS, THEY WILL LOSE RENAL FUNCTION. THIS IS A TRIAL FROM DR. CROWLEY THAT LOOKED AT PATIENTS ON FOLLOW-UP WHO HAD LESS THAN 50 PERCENT RENAL ARTERY STENOSIS WITH NORMAL RENAL FUNCTION. THOSE WHO PROGRESSED TO SEVERE RENAL ARTERY STENOSIS HAD ABNORMAL RENAL FUNCTION. SO A PROGRESSION, IF IT HAPPENS, IS ASSOCIATED WITH LOSS OF RENAL DISEASE. THEY DO NOT NECESSARILY NEED TO PROGRESS TO OCCLUSION TO HAVE THAT PROBLEM.

THIS IS DATA THAT REMINDS ME TO TELL YOU THAT THERE'S A DIFFERENCE BETWEEN STENTS AND ANGIOPLASTY. I FIND THAT PROVIDERS WHO ARE NOT IN THE INTERVENTIONAL ARENA COMMONLY BLEND THE WORD INTERVENTION, AND THINK THAT ANGIOPLASTY AND STENTS ARE THE SAME, AND THEY CLEARLY ARE NOT. SO WHEN YOU CONSIDER THIS DATA, YOU HAVE TO MAKE SURE YOU SEPARATE STENT DATA FROM THE ANGIOPLASTY DATA BECAUSE

00114

THEY ARE DIFFERENT, AND THERE IS GOOD EVIDENCE THAT STENT THERAPY DOES IMPACT POSITIVELY KIDNEY FUNCTION IN MULTIPLE STUDIES. THESE ARE NOT CONTROLLED STUDIES, THIS DOES NOT SAY THAT STENTS ARE BETTER THAN MEDICAL THERAPY OR ANY OTHER THERAPY, BUT IT DOES DEMONSTRATE TO YOU THAT THERE IS AN EFFECTIVE CHANGE IN RENAL FUNCTION AFTER STENTING.
THIS IS A META-ANALYSIS OF DATA THAT ADMITTEDLY, AS YOU'VE HEARD THIS MORNING, IS RELATIVELY WEAK AND CONTAMINATED DATA. BUT THE META-ANALYSIS ITSELF DEMONSTRATES THAT FOR RENAL FUNCTION MEASURED BY SERUM CREATININE, IT FAVORS BALLOON ANGIOPLASTY. IF WE LOOK AT CREATININE CLEARANCE, IT FAVORS BALLOON ANGIOPLASTY, STATISTICALLY SIGNIFICANT. AND IF WE LOOK AT MEDICINES VERSUS BALLOON, AGAIN, NOT STENTED, THE BALLOONS WOULD CONTROL HYPERTENSION, STATISTICALLY SIGNIFICANT. THE META-ANALYSIS OF THESE TRIALS THAT ARE ADMITTEDLY COMPROMISED AND FLAWED, BUT THE DATA CURRENTLY SUGGESTS THAT INTERVENTION WITH BALLOON ANGIOPLASTY STATISTICALLY IS BETTER THAN MEDICAL THERAPY.
YOU'VE HEARD ABOUT THE DRASTIC TRIAL. THE DRASTIC TRIAL IS SERIOUSLY FLAWED AGAIN, SINCE CROSSOVER WAS ALMOST HALF THE PATIENTS. BUT WHAT

00115

ISN'T OFTEN LOOKED AT IS WHAT HAPPENED TO THOSE PATIENTS AS THEIR OWN CONTROL. THE WAY THE DATA WAS REPORTED WAS AS A COMPARISON BETWEEN THE GROUPS OF INTERVENTION AND MEDICAL THERAPY, AND THERE WAS NO DIFFERENCE AT BASELINE, THERE WAS NO DIFFERENCE AT THREE MONTHS, AND THEN THE CROSSOVER OCCURRED. WHAT THEY DON'T TELL YOU IS THAT IF YOU COMPARE EACH GROUP AS ITS OWN CONTROL, THERE WAS STATISTICAL IMPROVEMENT IN THE BLOOD PRESSURE OF THE INTERVENTIONAL BALLOON ANGIOPLASTY GROUP COMPARED WITH THE MEDICAL GROUP. IT WAS THEN CAUGHT UP WITH THE 44 PERCENT CROSSOVER RATE.

THE SECOND RANDOMIZED CONTROLLED TRIAL, THE EMMA TRIAL DID DEMONSTRATE A SIGNIFICANT BENEFIT FOR DIASTOLIC BLOOD PRESSURE. YOU'VE HEARD THAT. IT WOULD HAVE DEMONSTRATED A BLOOD PRESSURE IMPROVEMENT FOR SYSTOLIC AS WELL IF THE NUMBER OF PATIENTS HAD BEEN LARGE ENOUGH, BECAUSE THE DIFFERENCE IS CERTAINLY LARGE.

AND THEN FOR BILATERAL DISEASED PATIENTS, IN THE THIRD RANDOMIZED CONTROLLED TRIAL, THIS IS THE SCOTTISH TRIAL, IT DID ACHIEVE STATISTICALLY SIGNIFICANT DIFFERENCE IN THAT BILATERAL SUBGROUP.

SO THERE ARE THREE RANDOMIZED TRIALS, ALL OF WHICH DEMONSTRATED STATISTICALLY SIGNIFICANT

00116

BENEFIT TO THE INTERVENTIONAL GROUP.
THIS IS A TRIAL THAT DEMONSTRATES THE DIFFERENCE BETWEEN STENTS AND BALLOONS. AGAIN, THIS WAS HAMPERED BY A 30 PERCENT CROSSOVER RATE IN THIS TRIAL, BUT IT DEMONSTRATES A PROCEDURE SUCCESS. THERE'S A SIGNIFICANT BENEFIT FOR STENTING OVER ANGIOPLASTY. AND FOR RESTENOSIS, AS YOU'VE HEARD, RESTENOSIS IS ALMOST 50 PERCENT FOR BALLOON ANGIOPLASTY AND IS IN THE MIDDLE TEENS FOR STENTING.
THESE ARE TO ADDRESS THE ISSUES OF THE DEFINITIONS. WE ACTUALLY SUBSCRIBE TO THE JNC-7.
FOR IMAGING METHODS AND TRANS-LESIONAL GRADIENTS, YOU SAW DR. SOS REPRESENT THIS DATA. THIS IS ELEGANT PHYSIOLOGY THAT DEMONSTRATES WHAT MANY OF US KNOW, AND AS DR. SOS SAID, IF A 10 PERCENT GRADIENT STARTS TO APPEAR, THEN RENIN IS INCREASED FROM THE AFFECTED KIDNEY. WHAT IS VERY IMPORTANT IS THAT THE UNAFFECTED KIDNEY ALSO SEES THIS SIGNAL AND PRODUCES RENIN.
SURGERY HAS BEEN RECENTLY ADDRESSED.
SURGERY IS NOT THE PREFERRED TREATMENT FOR RENAL ARTERY STENOSIS, AND SURGERY WOULD NOT BE A VERY EFFECTIVE THERAPY IF WE WENT BACK TO OUR HOSPITALS TODAY AND WERE NOT ABLE TO DO RENAL INTERVENTIONS.
SURGERY IS COMPLICATED BY INCREASED RISKS, ESPECIALLY

00117

IF THERE'S A NEED FOR AORTIC RECONSTRUCTION, IF THERE'S PRE-OP RENAL FAILURE, OR AN AORTIC GRAFT IS USED AS THE SOURCE, AND THERE ARE SOME PROBLEMS WITH SURGERY.

THE LONG-TERM DURABILITY OF STENTS HAS BEEN QUESTIONED. THERE ARE ACTUALLY TWO PAPERS THAT HAVE REPORTED LONG-TERM DURABILITY. THIS IS A PAPER BY HENRY IN 1999, WITH A PRIMARY PATENCY OF 78 PERCENT OUT MORE THAN FIVE YEARS AND A SECONDARY PATENCY OF OVER 95 PERCENT. SO CLEARLY THE DURABILITY OF STENTS AND THE RESTENOSIS RATE IS FAR BETTER THAN IT IS FOR ANGIOPLASTY.

FOR DIAGNOSTIC TESTS, WE HAVE EVIDENCE TO AGREE WITH WHAT DR. LINAS JUST SAID, AND THAT IS THAT THE MORE RAPID A PATIENT'S RENAL DECLINE IS, THE MORE LIKELY THEY WILL BENEFIT. WE'VE DONE SOME WORK AT OUR INSTITUTION IN NEW ORLEANS THAT SUGGESTS THAT THE RENAL FRACTIONAL FLOW RESERVE DOES PREDICT THE PATIENTS WHO ARE LIKELY TO BENEFIT FROM BLOOD PRESSURE, THEIR BLOOD PRESSURE WILL BENEFIT AFTER INTERVENTION WITH A STATISTICALLY SIGNIFICANT BENEFIT WITH FRACTIONAL FLOW RESERVE MEASURED IN THE RENAL ARTERY.

AGAIN, PATIENTS WHO HAD A FRACTIONAL FLOW RESERVE LESS THAN .8 HAD ALMOST A 90 PERCENT CHANCE

00118

OF BLOOD PRESSURE IMPROVEMENT. THIS IS A GREAT WAY TO SEPARATE PATIENTS WHO ARE BORDERLINE FOR INTERVENTION.

DR. GARBER: DR. WHITE, I'M GOING TO HAVE TO ASK YOU TO STOP. THANK YOU. DR. JAFF, AND HE WILL BE FOLLOWED BY DR. MISRA.

DR. JAFF: MR. CHAIRMAN, MEMBERS OF THE PANEL, LADIES AND GENTLEMEN, THANK YOU FOR THE OPPORTUNITY. MY NAME'S MICHAEL JAFF. I'M A VASCULAR MEDICINE PHYSICIAN AT MASSACHUSETTS GENERAL HOSPITAL IN BOSTON. I REPRESENT BOTH THE SOCIETY FOR VASCULAR MEDICINE BIOLOGY AND THE VIVA PHYSICIANS GROUP. MY TRAVEL TODAY WAS PAID FOR BY VIVA PHYSICIANS. I DO HAVE CONFLICTS TO INFORM YOU OF. I DO HAVE STOCK OWNERSHIP IN SQUARE ONE INCORPORATED AND PARAGON MEDICAL, AND I HAVE BEEN IN THE PAST OR AM CURRENTLY A CONSULTANT FOR CORDIS ENDOVASCULAR, BOSTON SCIENTIFIC AND MEDTRONIC. I HAVE SPOKEN TO THE SOCIETY FOR VASCULAR MEDICINE AND BIOLOGY, THE VIVA GROUP, AND THE SOCIETY FOR CARDIAC ANGIOGRAPHY INTERVENTION ABOUT THIS SPECIFIC MEETING PRIOR TO THIS DISCUSSION TODAY.

WITH SOME BACKGROUND, THE SOCIETY FOR VASCULAR MEDICINE AND BIOLOGY IS THE ONLY PROFESSIONAL MEDICAL SOCIETY OF INTERNISTS WHO

00119

DIAGNOSE AND MEDICALLY MANAGE PATIENTS WITH ALL ASPECTS OF VASCULAR DISEASE, INCLUDING RENAL ARTERY DISEASE. VIVA PHYSICIANS IS A NOT-FOR-PROFIT ORGANIZATION OF TEN SPECIALISTS IN VASCULAR DISEASE, INCLUDING VASCULAR SURGERY, INTERVENTIONAL CARDIOLOGY, INTERVENTIONAL RADIOLOGY AND VASCULAR MEDICINE, ALL DEDICATED TO RESEARCH AND EDUCATION IN VASCULAR DISEASE.

I PERSONALLY ACT AS THE MEDICAL DIRECTOR OF THE VASCULAR ULTRASOUND CORE LABORATORY FOR THE CORAL TRIAL, AND I AM A NONINTERVENTIONAL PHYSICIAN. THEREFORE, MY INTEREST IN THIS FIELD IS IN THE MANAGEMENT OF PATIENTS WITH RENAL ARTERY DISEASE.

ONE IMPORTANT POINT TO NOTE AS YOU'VE HEARD DISCUSSIONS ABOUT MEDICAL THERAPY FOR RENAL ARTERY DISEASE IS THAT THERE REALLY IS NO SPECIFIC DATA DEMONSTRATING THE EFFICACY OF STATINS, ANTILIPID AGENTS OR DIABETES CONTROL AGENTS IN PATIENTS SPECIFICALLY WITH RENAL ARTERY DISEASE. IN ADDITION, MANY PATIENTS WE CARE FOR IN MEDICINE IN THE FIELD OF RENAL ARTERY DISEASE, CARDIOVASCULAR MEDICINE, AND OUTSIDE OF THIS FIELD IN MEDICINE, ARE TREATED WITHOUT LEVEL I RANDOMIZED CONTROLLED DATA, AND WE MAKE DECISIONS AS PHYSICIANS BASED ON THE BEST EVIDENCE THAT EXISTS.

00120

WE DO HAVE EXTENSIVE CLINICAL EXPERIENCE IN THE SAFETY OF RENAL ENDOVASCULAR REVASCULARIZATION. I AGREE WITH DR. WHITE AND OTHERS THAT BALLOON ANGIOPLASTY IS NOT STATE OF THE ART THERAPY FOR THIS DISORDER, AND FRANKLY, SHOULD NOT BE CONTINUED IN DISCUSSIONS ABOUT THE TREATMENT OF ATHEROSCLEROTIC RENAL ARTERY STENOSIS. IN ADDITION, WE DO NOT BELIEVE THAT THERE IS ANY DRUG-ELUTING STENT DATA IN RENAL ARTERY DISEASE THAT WOULD OFFER ANY WORTHY DISCUSSION, AND THEREFORE, WE NOT CONTINUE ON THAT EITHER.

REGARDING SURGICAL RENAL REVASCULARIZATION, WE BELIEVE THAT THIS CARRIES SIGNIFICANT PERIPROCEDURAL MORBIDITY AND MORTALITY, AND EXCEPT FOR VERY SELECTIVE SCENARIOS, SHOULD NOT BE USED AS A PRIMARY REVASCULARIZATION STRATEGY IN 2007 AND BEYOND. THIS IS NOT A SIMILAR DISCUSSION TO THAT OF PROVIDED ENDARTERECTOMY VERSUS CAROTID ENDOVASCULAR THERAPY, AND IN FACT I WOULD SUBMIT TO YOU THAT THERE ARE MANY SKILLED VASCULAR SURGEONS, NEUROSURGEONS AND EVEN OTHER SURGICAL SPECIALISTS, WHO PERFORM EXCELLENT CAROTID ENDARTERECTOMY. HOWEVER, I FEAR THAT AS THE NUMBER OF SURGICAL REVASCULARIZATIONS FOR RENAL ARTERY DISEASE DECLINE, THAT THE NUMBER OF TRAINEES COMING OUT OF

INSTITUTIONS WITH EXCELLENT TRAINING PROGRAMS IN VASCULAR SURGERY, WE WILL NOT BE ABLE TO SAY THE SAME FOR RENAL ARTERY SURGERY REVASCULARIZATION.

WE STRONGLY SUPPORT THE ENROLLMENT IN THE CORAL TRIAL. HOWEVER, THERE ARE IN FACT A NUMBER OF PATIENTS WHO WOULD NOT BE ELIGIBLE TO PARTICIPATE IN CORAL FOR A NUMBER OF REASONS, AND OTHER RANDOMIZED PROSPECTIVE TRIALS. IN ADDITION, THERE ARE 100 SITES THAT ARE PARTICIPATING IN THE CORAL TRIAL IN THE UNITED STATES AND OUTSIDE THE UNITED STATES, AND THAT DOES NOT ALLOW FOR WIDESPREAD USE IF THERE WERE ANY CONSIDERATION TO RESTRICTING REIMBURSEMENT FOR PATIENTS ONLY IN RANDOMIZED CLINICAL TRIALS.

IN AN EFFORT TO EXPAND THE KNOWLEDGE BASE, VIVA PHYSICIANS IS ANNOUNCING THAT WE ARE WORKING ON A PERFORMANCE GOAL INITIATIVE USING A MODERN DATABASE OF OVER 500 PATIENTS THAT HAVE BEEN ENROLLED IN PROSPECTIVE FDA-APPROVED CLINICAL TRIALS. WE CLEARLY AGREE THAT WE NEED TO DO OUR BEST TO MANAGE THESE COMPLEX PATIENTS WITH REFRACTORY AND RESISTANT HYPERTENSION, GLOBAL RENAL ISCHEMIA WITH BASELINE AZOTEMIA, DIALYSIS-DEPENDENT RENAL FAILURE DUE TO RENAL ARTERY DISEASE, ESPECIALLY WITH RAPID DETERIORATION OF RENAL FUNCTION, AND NOT PROPHYLACTIC STENTING. WE SUPPORT DR. SOS'S COMMENTS.

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AND FINALLY, WE DO NOT BELIEVE THAT THERE IS SIGNIFICANT DATA IN THE LITERATURE TO JUSTIFY ANY CHANGE IN THE REIMBURSEMENT SCHEME FOR RENAL ARTERY DISEASE, AND UNTIL THE CORAL TRIAL AND OTHERS COMPLETE, WE WOULD URGE CONTINUED VIGILANCE IN THIS FIELD. THANK YOU FOR THE OPPORTUNITY.

DR. GARBER: THANK YOU, DR. JAFF. NEXT, DR. MISRA, AND HE WILL BE FOLLOWED BY DR. HIRSCH.

DR. MISRA: GOOD MORNING. I'M AN INTERVENTIONAL RADIOLOGIST AT THE MAYO CLINIC. MY TRAVEL HERE WAS PAID BY THE MAYO CLINIC AND I RECEIVE AN HONORARIUM TO SERVE ON THE ADVISORY PANEL FOR CORDIS.

WHAT I'M HERE TO TALK ABOUT TODAY IS SOME DATA THAT HASN'T BEEN PUBLISHED, TALKING A LITTLE BIT ABOUT HOW DO PATIENTS DO THAT HAVE ENDOVASCULAR TREATMENT OF RENAL ARTERY STENOSIS IN A SETTING OF RENAL SUFFICIENCY. THIS DATA STARTED ABOUT TWO YEARS AGO, A DATABASE THAT WAS ACCUMULATED AT THE MAYO CLINIC, AND I'M GOING TO GO THROUGH SOME OF THIS RATHER QUICKLY SO I CAN ADHERE TO MY SIX MINUTES.

MOVING RIGHT INTO -- THE REASON WE STARTED LOOKING AT THIS WAS, HERE'S A PATIENT WHO CAME INTO THE CLINIC AND WAS SEEN BY MYSELF, A NEPHROLOGIST AND OTHERS. AND THE QUESTION WAS, HE'S HYPERTENSIVE,

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HE'S ON THREE MEDICATIONS, HE'S GOT PROGRESSIVE RENAL SUFFICIENCY, HE'S GOT DIABETES, HE'S GOT PERIPHERAL ATHEROSCLEROTIC DISEASE, AND I'LL SHOW YOU TWO MRAS FOUR YEARS APART WHICH BASICALLY SHOW THAT HE'S GOT BILATERAL RENAL ARTERY STENOSIS.

NOW WHAT WAS THE BEST MANAGEMENT FOR THIS GENTLEMAN? IN 2003 HE HAD A GFR ESTIMATED AT THAT TIME OF ABOUT 40. FOUR YEARS LATER, THE SAME GFR.

WHAT'S INTERESTING IS IF YOU LOOKED AT HIS URINE, AND I KNOW THERE'S A LOT OF NEPHROLOGISTS HERE, THE PROTEINURIA CHANGED. IN 2003 HE HAD A MILD AMOUNT OF PROTEINURIA, ABOUT 300 MILLIGRAMS IN 24 HOURS. BY 2007 THAT HAD PROGRESSED TO MORE THAN A GRAM.

SO WHAT'S INTERESTING TO ME AS A RADIOLOGIST IS THAT OVER THE LAST TWO YEARS, THE CHRONIC KIDNEY INITIATIVE HAS RECLASSIFIED LOOKING AT CHRONIC KIDNEY DISEASE, AND THESE NUMBERS ARE NOT ACCURATE, THEY SHOULD BE 90 HERE AND 90 HERE, BUT I WANT TO FOCUS OUR ATTENTION ON STAGE 3, 4 AND 5 DISEASE, AND THIS IS WHAT WE WANTED TO LOOK AT. IF YOU HAVE STAGE 3, 4 AND 5 DISEASE AND YOU HAVE RENAL ARTERY STENOSIS AND WE STENTED YOU, WHAT WERE YOUR OUTCOMES?

AND HOW DID WE GET AT THIS? WE REVIEWED OUR EXPERIENCE AT SCOTTSDALE, JACKSONVILLE AND

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ROCHESTER FROM '96 TO 2005, AND CLASSIFIED EVERYBODY INTO A STAGE FOR CHRONIC KIDNEY DISEASE, BASICALLY 1, 2, 3, 4 AND 5. AND THE OUTCOMES THAT I WAS MOST INTERESTED IN, AND MANY OF YOU HAVE ALLUDED TO IT, IS WHAT'S MOST IMPORTANT TO ME WAS DID YOU DIE, DID YOU GET TRANSPLANTED, OR DID YOU GO INTO DIALYSIS. THE WAY OUR PRACTICE RUNS, IT'S A VERY TRANSIENT PRACTICE, PEOPLE COME AND GET TREATED AND GO BACK HOME. WE'VE SENT FOR THE U.S. RENAL DATA SYSTEM WITH DIALYSIS TRANSPLANTATION DATA, AND WE'VE GOT THE DEATHS FROM THE SOCIAL SECURITY DATABASE, AND WE LOOKED THROUGH ALL THE ANGIOGRAPHIC CLINICAL DATA SETS. THE OTHER THING WE DID WAS WE CLASSIFIED EVERYBODY INTO A STAGING PHASE BASED ON A MODIFICATION OF DIET RENAL DISEASE FORMULA, AND ALSO DETERMINED THE 24-HOUR PROTEINURIA.
WE HAVE TREATED IN THIS TIME PERIOD APPROXIMATELY 1,500 PATIENTS. WE HAD 700 PATIENTS THAT FELL INTO THIS GROUPING, AND THE DATA THAT I'M GOING TO SHOW YOU IS BASED ON LIFE TABLE ESTIMATES AFTER MULTIVARIATE-UNIVARIATE ANALYSIS ON 552 PATIENTS. THE REST OF IT IS PENDING.
THIS IS WHAT THE BREAKDOWN WAS. WE DIVIDED STAGE 3, I FOUND IT TO BE TOO LARGE OF A STAGE, INTO 3-A AND 3-B. AND WE HAD ABOUT 165

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PATIENTS, 190, IN STAGE 4 AND STAGE 5. WHAT WE FOUND WAS BASED ON STAGING AND PROTEINURIA AND DIABETES, WE HAD DIFFERENT OUTCOMES. WHAT I'M GOING TO SHOW YOU IS BASICALLY FIVE-YEAR SURVIVAL ESTIMATES FROM THIS DATA.

SO THESE WERE THE COMORBIDITIES. I'M GOING TO FLY THROUGH HERE SO I DON'T GET CUT OFF.

AND THIS WAS OUR FIRST SLIDE. THERE WAS SIGNIFICANT SURVIVAL DIFFERENCE, AND THIS WAS FOR A COMPOSITE OF DEATH AND FREEDOM FROM DIALYSIS OR TRANSPLANTATION FOR FIVE YEARS. THERE'S A P VALUE. THE PEOPLE DID DIFFERENTLY IF YOU CAME IN WITH DIFFERENT GFRS. SO WE BASICALLY KNEW THAT, OR WE HAD A GOOD IDEA OF THAT.

BUT IF YOU LOOKED AT DIFFERENCES IN DIABETICS VERSUS NONDIABETICS, WE HAD A SMALL GROUP OF DIABETICS HERE, THERE WASN'T A DIFFERENCE. BUT WHEN YOU GOT INTO STAGE 3-B, DIABETICS VERSUS NONDIABETICS, THERE WAS A DIFFERENCE, AGAIN, SIGNIFICANT VALUE BY P VALUE AT FIVE YEARS, AND THIS IS THE STAGING.

NOW LOOKING AT LOW AND HIGH PROTEINURIA, WE DEFINED LOW PROTEINURIA AS 300 MILLIGRAMS IN 24 HOURS OR LESS, AND THERE WERE DIFFERENCES. SAME HERE, 3-A AND 3-B. SO DEPENDING ON GFR, PROTEINURIA

WAS A TRUMP CARD AND SO WAS DIABETES. YOU CAN MOVE IN AND LOOK AT THESE CURVES, AND WE'VE SUPERIMPOSED DIABETES WITH LOW AND HIGH PROTEINURIA, NONDIABETICS WITH LOW AND HIGH PROTEINURIA. THE P VALUES, FIVE-YEAR ESTIMATES FOR ALL THREE SURVIVAL, FOR DEATH, DIALYSIS FREE SURVIVAL, TRANSPLANTATION, WHAT A DIFFERENCE.

MOVING TO STAGE 4, NOT A LOT OF DIFFERENCE BETWEEN DIABETES AND NONDIABETES, AND IN PART WE HAD LOW NUMBERS OF DIABETICS. THIS WAS AGAIN A RETROSPECTIVE STUDY. YOU CAN SEE WHAT THE SURVIVAL CURVES ARE. FOR GFR BETWEEN LOW AND HIGH PROTEINURIA, AGAIN, SIGNIFICANT DIFFERENCES IF YOU WERE DROPPING PROTEIN. AND THIS IS WHAT THE CURVES LOOKED LIKE SUPERIMPOSED WITH DIABETES WITH LOW AND HIGH PROTEINURIA, SIGNIFICANT DIFFERENCES.

FINALLY, STAGE 5, A SMALL GROUP, WE HAD ABOUT 40 PATIENTS. THESE WERE ALL PEOPLE THAT WERE NOT ON DIALYSIS YET. NO DIFFERENCE IN SURVIVAL BASED ON DIABETES OR NONDIABETES. MOVING TO LOW AND HIGH PROTEINURIA, NOT A BIG DIFFERENCE BECAUSE THE N WAS SMALL.

SO I THINK, YOU KNOW, WHAT I'VE TAKEN AWAY FROM THIS DATA IS, ONE, AN APPRECIATION FOR PICKING THE PATIENTS. BASELINE GFR IS A STRONG PREDICTOR,

PROTEINURIA IS A STRONG PREDICTOR, DIABETES IS A STRONG PREDICTOR FOR A COMPOSITE SURVIVAL, FIVE-YEAR ESTIMATES FOR THIS.

ONE OF THE WEAKNESSES OF OUR DATA IS THAT WE DON'T HAVE A CONTROL STUDY. WE'RE SUPPOSED TO BE GETTING ABOUT 400 TO 500 PATIENTS FROM ENGLAND FROM DR. KALERA, WHO HAS FOLLOWED PATIENTS WITH SIMILAR OUTCOMES, AND WE WILL TRY TO MATCH THEM UP IN A CASE CONTROL SETTING. THANK YOU.

DR. GARBER: THANK YOU, DR. MISRA. NEXT WILL BE DR. HIRSCH, AND HE WILL BE FOLLOWED BY DR. ZWOLAK.

DR. HIRSCH: PANEL AND COLLEAGUES, THANK YOU FOR THE OPPORTUNITY TO PRESENT THE VIEWS OF THE AMERICAN HEART ASSOCIATION. AND FOR INTRODUCTION, MY NAME IS DR. ALAN HIRSCH. I SERVE AS PROFESSOR OF EPIDEMIOLOGY AND COMMUNITY HEALTH AT THE UNIVERSITY OF MINNESOTA SCHOOL OF PUBLIC HEALTH, AND DIRECTOR OF ABBOTT NORTHWESTERN VASCULAR CENTER IN MINNEAPOLIS, MINNESOTA. I HAVE SERVED AS CHAIR OF THE ACC/AHA WRITING COMMITTEE TO DEVELOP GUIDELINES FOR THE MANAGEMENT OF PATIENTS WITH PERIPHERAL ARTERIAL DISEASE.

IN THE INTEREST OF FULL DISCLOSURE, AHA RECEIVES LESS THAN ONE PERCENT OF ITS REVENUE FROM

PHARMACEUTICAL AND MEDICAL DEVICE INDUSTRIES.
PERSONALLY I SERVE AS AN ACTIVE INVESTIGATOR IN A
NUMBER OF CARDIOVASCULAR CLINICAL RESEARCH STUDIES,
INCLUDING THE CORAL STUDY. HOWEVER, I DO NOT SERVE
IN ANY CONSULTING CAPACITY NOR RECEIVE FINANCIAL
SUPPORT FROM ANY STENT MANUFACTURING COMPANY.
NEITHER THE ASSOCIATION NOR I RECEIVED ANY SPECIFIC
FUNDING TO PARTICIPATE IN TODAY'S MEETING.
MY TESTIMONY IS BASED PRIMARILY ON THE
ACC/AHA 2005 PRACTICE GUIDELINES FOR THE MANAGEMENT
OF PATIENTS WITH PERIPHERAL ARTERIAL DISEASE,
INCLUDING LOWER EXTREMITY, RENAL, MESENTERIC, AND
ABDOMINAL AORTIC DISEASE, AND MY COMMENTS WILL BE
OBVIOUSLY MUCH ABBREVIATED FROM THE MARCH 28 LETTER
SUBMITTED TO CMS.
THESE GUIDELINES HAVE BEEN CO-DEVELOPED IN
A PROCESS BEGINNING OVER 25 YEARS AGO IN 1980. IT
INVOLVES A RIGOROUS SYSTEMATIC REVIEW OF THE BEST
PRINTED SCIENTIFIC EVIDENCE. A BRIEF OVERVIEW OF THE
GUIDELINES DEVELOPMENT PROCESS IS PRESENTED IN THIS
SLIDE, AND THE GUIDELINE THAT I WILL DISCUSS TODAY
WAS CHARTERED IN ORDER TO ASSIST HEALTHCARE PROVIDERS
WITH THE CLINICAL DECISION-MAKING, WHICH IS COMPLEX,
REQUIRED FOR MAKING THE DIAGNOSIS, MANAGING AND
PREVENTING THE THREE MAJOR CLINICAL MANIFESTATIONS OF

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PAD, INCLUDING ATHEROSCLEROTIC RENAL ARTERY STENOSIS. THESE GUIDELINES FOR RENAL ARTERY STENOSIS IN PAD WERE DEVELOPED BY ACC AND THE AHA IN COLLABORATION WITH THE SOCIETY FOR VASCULAR SURGERY, THE SOCIETY FOR CARDIOVASCULAR ANGIOGRAPHY INTERVENTION, THE SOCIETY FOR VASCULAR MEDICINE AND BIOLOGY, THE SOCIETY OF INTERVENTIONAL RADIOLOGY, AND AGAIN, NOT FOCUSED ON THIS SLIDE, AS WELL AS THESE ADDITIONAL FIVE ORGANIZATIONS WHICH PERFORMED A CLOSE PEER REVIEW AND ENDORSED THIS GUIDELINE, INCLUDING THE NATIONAL HEART, BLOOD AND LUNG INSTITUTE. THESE WERE THE FIRST MAJOR NATIONAL TREATMENT GUIDELINES FOR RENAL ARTERY STENOSIS EVER PUBLISHED, AND THEY DO REPRESENT THE WIDEST PROFESSIONAL ENDORSEMENT AND CONSENSUS EVER ACHIEVED FOR ANY VASCULAR CARE EVIDENCE-BASED GUIDELINE. MANY OF YOU WILL BE FAMILIAR WITH THE METHODS USED FOR THESE GUIDELINES SUMMARIZED IN THIS SLIDE. IN CONSIDERING APPROACHES TO IDENTIFYING PATIENTS WITH RENAL ARTERY STENOSIS WHO WOULD BENEFIT FROM TREATMENT, THE GUIDELINES ASSIGN A CLASSIFICATION OF EACH RECOMMENDATION. A CLASS I RECOMMENDATION, WHICH INDICATES THAT THERE IS EVIDENCE AND/OR GENERAL AGREEMENT THAT A GIVEN PROCEDURE OR TREATMENT IS BENEFICIAL, USEFUL AND

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EFFECTIVE, IS THE HIGHEST LEVEL OF EVIDENCE.
CLASS II RECOMMENDATIONS ARE OBVIOUSLY NOT AS STRONG
AND MAY REPRESENT CONFLICTING EVIDENCE OR DIVERGENCE
OF OPINIONS. AND CLASS III RECOMMENDATIONS CLEARLY
CAN DEMONSTRATE AREAS WHERE THERE IS GENERAL
AGREEMENT THAT A PROCEDURE IS NOT BENEFICIAL OR MAY
BE HARMFUL.
AND THEN EACH CLASS IS OF COURSE
IDENTIFIED WITH A SPECIFIC LEVEL OF EVIDENCE UPON
WHICH THE RECOMMENDATION IS BASED. LEVEL A BEING THE
HIGHEST LEVEL, REPRESENTING INFORMATION FROM MULTIPLE
RANDOMIZED TRIALS, LEVEL B INDICATING A SINGLE
RANDOMIZED TRIAL OR NONRANDOMIZED STUDIES, AND
LEVEL C REPRESENTING GENERALLY OPINION OF EXPERTS,
CASE STUDIES, OR THE CURRENT STANDARD OF CARE.
NOW BASED ON THE EVIDENCE CURRENTLY
AVAILABLE, THE GUIDELINES MADE THE FOLLOWING CLASS I
AND IIA RECOMMENDATIONS FOR THE TREATMENT OF
ATHEROSCLEROTIC RENAL ARTERY STENOSIS, AND I WILL TRY
TO BE BRIEF IN SUMMARIZING THESE. THESE ARE
OBVIOUSLY AVAILABLE TO THE PANEL FOR THEIR REVIEW.
THE GUIDELINES ENDORSE THE PHARMACOLOGIC TREATMENT
FOR ALL INDIVIDUALS WITH ATHEROSCLEROTIC RENAL ARTERY
STENOSIS, INCLUDING EACH OF THE VARIOUS CLASS OF
MEDICATIONS THAT HAS ALREADY BEEN REVIEWED BY THE

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PRIOR PRESENTERS. WE DO BELIEVE THAT CLINICIANS SHOULD CONSIDER MEDICAL THERAPY FOR THE TREATMENT OF HYPERTENSION ASSOCIATED WITH ALL PATIENTS WITH UNILATERAL RENAL ARTERY STENOSIS.
AND WE KNOW THAT THESE ARE CLASS I RECOMMENDATIONS, WITH THE EXCEPTION OF THAT FOR ANGIOTENSIN RECEPTOR BLOCKERS, WHICH WAS BASED ON DATA FROM A SINGLE TRIAL OR STUDY. BEYOND THAT, ALL THE RECOMMENDATIONS FOR MEDICAL THERAPY WERE BASED ON DATA FROM MULTIPLE RANDOMIZED CLINICAL TRIALS OR META-ANALYSES.
FOR ANGIOPLASTY AND STENTING, WE DID RECOGNIZE A MUCH MORE LIMITED DATABASE FOR THE TREATMENT OF ATHEROSCLEROTIC RENAL ARTERY STENOSIS BY ENDOVASCULAR APPROACHES. BUT WE DID RESPECT THE STILL SUBSTANTIAL EVIDENCE SUPPORTING ITS EFFICACY.
THE CURRENT EVIDENCE BASE, ALTHOUGH LIMITED, DOES SUGGEST THAT REVASCULARIZATION COULD BENEFIT SELECTED PATIENTS WITH ATHEROSCLEROTIC RAS. FOR EXAMPLE, THE GUIDELINE DOES SUGGEST THAT PHYSICIANS CONSIDER PERCUTANEOUS REVASCULARIZATION IN PATIENTS WITH HEMODYNAMICALLY SIGNIFICANT RAS WHOSE STENOSIS IS ASSOCIATED WITH RECURRENT, UNEXPLAINED CONGESTIVE HEART FAILURE, SUDDEN UNEXPLAINED PULMONARY EDEMA, OR UNSTABLE ANGINA.

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WE ALSO RECOGNIZED IN THIS GUIDELINE THAT PHYSICIANS CONSIDER PERCUTANEOUS REVASCULARIZATION IN PATIENTS IN WHOM THERE IS A PHYSIOLOGICALLY SIGNIFICANT RAS AND ACCELERATED, RESISTANT, OR MALIGNANT HYPERTENSION, WELL DEFINED IN THE WRITTEN TEXT, HYPERTENSION WITH UNEXPLAINED SMALL UNILATERAL KIDNEY, AS WELL AS INDIVIDUALS WITH HYPERTENSION INTOLERANT TO MEDICATION, OR PATIENTS WITH PROGRESSIVE CHRONIC KIDNEY DISEASE AND BILATERAL ATHEROSCLEROTIC RAS, AS WELL AS INDIVIDUALS WITH ATHEROSCLEROTIC RAS IN A SOLITARY FUNCTIONING KIDNEY. THESE RECOMMENDATIONS WERE ALSO ALL CLASS I OR IIA, LEVEL OF EVIDENCE B, AND BASED ON THE EVIDENCE AVAILABLE, WE WOULD SUGGEST THAT THESE SPECIFIC PATIENT GROUPS ARE CURRENTLY QUITE APPROPRIATE FOR COVERAGE OF RENAL PTA. SURGICAL REVASCULARIZATION IS ALSO AN EFFECTIVE, IF MORE INVASIVE, TREATMENT AND SHOULD BE CONSIDERED FOR PATIENTS IN A NUMBER OF SITUATIONS, INCLUDING THOSE OUTLINED IN THIS SLIDE. FMD WITH CLINICAL INDICATIONS FOR INTERVENTIONS AS DEFINED ABOVE, AND THOSE AS OUTLINED IN THESE THREE BULLET POINTS EXHIBITING COMPLEX LESIONS EXTENDING INTO THE RENAL SEGMENTAL ARTERIES AND THOSE IN INDIVIDUALS HAVING MACROANEURYSMS, INDIVIDUALS WITH MULTIPLE

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SMALL RENAL ARTERIES OR EARLY PRIMARY BRANCHING OF THE MAIN RENAL ARTERY, AND INDIVIDUALS WHO HAVE UNDERGONE PARARENAL AORTIC RECONSTRUCTION FOR TREATMENT OF ANEURYSMS OR SEVERE AORTOILIAC DISEASE. ALL THREE REPRESENT CLASS I RECOMMENDATIONS SUPPORTED BY LEVEL OF EVIDENCE B OR C, AND WE STRONGLY SUPPORT COVERAGE FOR THESE CLASS I RECOMMENDATIONS.

DR. GARBER: DR. HIRSCH, I'LL HAVE TO ASK YOU TO STOP. THANK YOU VERY MUCH, BUT YOUR TIME IS UP. BUT LET ME JUST POINT OUT THAT I BELIEVE THE MEMBERS OF THE PANEL HAVE THIS IN THEIR BOOKS AND ALSO IN THE HANDOUTS FROM TODAY.

DR. HIRSCH: MAY I JUST MAKE THE STATEMENT THAT WE OBVIOUSLY SUPPORT ALIGNMENT OF INCENTIVES FOR CLINICAL TRIAL PARTICIPATION. THAT'S IMPORTANT AND YOU HAVE THAT IN YOUR BOOKS. THANK YOU VERY MUCH.

DR. GARBER: THANK YOU. DR. ZWOLAK WILL BE FOLLOWED BY DR. KELLEY.

DR. ZWOLAK: THANKS VERY MUCH. I'M BOB ZWOLAK. I CHAIR THE HEALTH POLICY COMMITTEE FOR THE SOCIETY FOR VASCULAR SURGERY. I HAVE NO CONFLICTS, BUT SVS PAID FOR MY TRANSPORTATION HERE, AND A DELIGHTFUL EVENING LAST NIGHT AT THE HOLIDAY INN. THE SVS REPRESENTS 2,300 PHYSICIANS IN THE

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UNITED STATES WHO HAVE BEEN TREATING RENOVASCULAR DISEASE FOR 40 YEARS. SVS IS IN A UNIQUE POSITION TO COMMENT ON RENAL ARTERY PDA AND STENTING, GIVEN OUR COMMUNITY'S HISTORY OF TREATING THIS PROCESS. WHILE OPEN SURGICAL REVASCULARIZATION IS NOT THE CENTRAL FOCUS OF THIS SESSION, A BRIEF REVIEW OF THE REFERENCES SVS SUBMITTED MAKES THE POINT THAT SURGICAL REVASCULARIZATION REALLY HAS BEEN THE STANDARD OF TREATMENT FOR THIS DISORDER FOR MANY YEARS, BUT THAT STANDARD IS CHANGING.

SINCE EIGHT TO 15 PERCENT OF PATIENTS WHO DEVELOP END-STAGE RENAL DISEASE HAVE ATHEROSCLEROTIC RENOVASCULAR DISEASE AS THE ONLY DOCUMENTED PATHOLOGY, WE BELIEVE TREATMENT OF THIS ENTITY IS COMPELLING. NATURAL HISTORY STUDIES HAVE SHOWN THAT ATHEROSCLEROTIC RENAL DISEASE TENDS TO PROGRESS OVER TIME, KIDNEYS WITH STENOTIC RENAL ARTERIES UNDERGO ATROPHY OR DETERIORATION OF RENAL FUNCTION. WHILE WE CAN CONTROL BLOOD PRESSURE SUCCESSFULLY IN ALMOST EVERY PATIENT NOW, THE UNFORTUNATE END POINT OF ATHEROSCLEROTIC RENAL DISEASE IS END-STAGE RENAL FAILURE IN A SUBSTANTIAL PROPORTION OF PATIENTS. THE KDOQI GUIDELINES STRESSED THE IMPORTANCE OF RENAL PRESERVATION AND THE BENEFITS ARE CLEAR AND NUMEROUS. THE OPEN SURGICAL DATA HAVE BEEN NICELY

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SUMMARIZED BY HANSEN, CAMBRIA AND OTHERS AND ARE IN THE RECORDS THAT WE SUPPLIED. THE SURGICAL LITERATURE HAS SHOWN EXCELLENT DURABILITY OF OPEN SURGICAL REVASCULARIZATION IN STABILIZING OR IMPROVING RENAL FUNCTION, BUT THIS IS DERIVED AT A SIGNIFICANT COST IN TERMS OF PERIOPERATIVE MORBIDITY AND MORTALITY. NEVERTHELESS, AT CENTERS OF EXCELLENCE, HYPERTENSION CAN BE CURED OR IMPROVED IN 85 PERCENT OF ATHEROSCLEROTIC ADULTS, WITH RENAL FUNCTION AMONG PATIENTS WITH ISCHEMIC NEPHROPATHY DEMONSTRATING A 20 PERCENT OR GREATER INCREASE IN GFR IN APPROXIMATELY 60 PERCENT OF PATIENTS. HANSEN'S SERIES IN FACT INCLUDED 28 OF 35 PATIENTS WHO WERE PERMANENTLY REMOVED FROM HEMODIALYSIS BY SURGICAL REVASCULARIZATION.

SO WHERE DOES PERCUTANEOUS INTERVENTION FIT BETWEEN MEDICAL THERAPY AND SURGICAL REVASCULARIZATION? STUDIES SUCH AS THE CORAL WILL PROVIDE INSIGHT BUT RECRUITMENT HAS BEEN SLOW, AND THAT BRINGS ABOUT ITS OWN SET OF ISSUES. I THINK IT'S IMPORTANT TO CITE THE DIFFERENCE IN APPROACH BY VASCULAR SURGEONS NOW COMPARING CAROTID STENTING WITH RENAL STENTING. AFTER TREATING RENOVASCULAR DISEASE FOR DECADES WITH OPEN SURGERY, THE VASCULAR SURGICAL COMMUNITY HAS EMBRACED THE BENEFITS OF RENAL STENTING

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COMPARED TO THE MAJOR OPEN OPERATIONS NECESSARY TO TREAT RENAL ARTERY STENOSIS. THE DIFFERENCE IN ATTITUDE BETWEEN CAROTID STENTING AND RENOVASCULAR DISEASE RELATES TO THE MAGNITUDE OF THE SURGERY FOR RENOVASCULAR DISEASE, AND IT'S SUBSTANTIAL.

SO WHAT SHOULD THE INDICATIONS BE FOR STENTING? THE STANDARD INDICATIONS FOR OPEN SURGERY FOR MANY YEARS HAVE INCLUDED POORLY CONTROLLED HYPERTENSION ON THREE MEDICATIONS, OR PROGRESSIVE ISCHEMIC NEPHROPATHY IN THE PRESENCE OF A SEVERE RENAL ARTERY STENOSIS. IF THREE-DRUG HYPERTENSION IS AN INDICATION FOR OPEN SURGERY, WHAT SHOULD CONSTITUTE AN APPROPRIATE INDICATION FOR STENT PLACEMENT? PROBABLY LESS THAN THAT, BUT STUDIES SUCH AS CORAL MAY HELP US DECIDE THAT.

SVS DOES NOT SUPPORT, HOWEVER, WHAT'S BEEN DESCRIBED THIS MORNING AS PROPHYLACTIC STENTING. WHILE I AND MANY OF MY COLLEAGUES ARE VERY SKILLED AT PERFORMING RENAL ARTERY BYPASS, WE WOULD TODAY RECOMMEND RENAL STENT PLACEMENT OVER RENAL BYPASS IN A PATIENT WITH POORLY CONTROLLED HYPERTENSION OR PROGRESSIVE RENAL NEPHROPATHY WITH A SEVERE PROXIMAL RENAL ARTERY STENOSIS.

NOW FOR MY LAST FEW MINUTES, I'D LIKE TO ADDRESS SPECIFICALLY SOME OF THE QUESTIONS. MANY OF

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THESE STUDIES HAVE BEEN CITED ALREADY. FIRST, IS THERE A CORRELATION BETWEEN PERCENT RENAL ARTERY STENOSIS AND RENAL FUNCTION? THE OBVIOUS ANSWER IS YES. IN THE CAPS STUDY, WHICH WAS A PROSPECTIVE NATURAL HISTORY STUDY UNDERTAKEN AT THE UNIVERSITY OF WASHINGTON, 170 PATIENTS WITH RENAL ARTERY STENOSIS GREATER THAN 60 PERCENT WERE FOLLOWED FOR A MEAN OF 33 MONTHS. HEMODYNAMIC PROGRESSION OF DISEASE WAS SEEN IN 31 PERCENT OF THE 295 ARTERIES STUDIED. NINE OF THE 295, OR THREE PERCENT, PROGRESSED TO COMPLETE OCCLUSION. THE INCIDENCE OF RENAL ATROPHY AT TWO YEARS, HOWEVER, WAS MUCH MORE SUBSTANTIAL; 21 PERCENT OF THE KIDNEYS WITH GREATER THAN 60 PERCENT STENOSIS DEMONSTRATED RENAL ATROPHY.

A STATISTICALLY SIGNIFICANT ASSOCIATION WAS NOTED BETWEEN THE NUMBER OF KIDNEYS PER PATIENT THAT SHOWED ATROPHY AND THE OBSERVED CHANGE IN THE SERUM CREATININE CONCENTRATION. THE MEAN CHANGE OF SERUM CREATININE LEVEL WAS ABOUT 0.1 MILLIGRAMS PER DECILITER PER YEAR AMONG PATIENTS WITH ATROPHY DETECTED IN ONLY ONE KIDNEY, BUT IT WAS SUBSTANTIALLY GREATER, MORE THAN 0.3 MILLIGRAMS PER DECILITER PER YEAR FOR THOSE PATIENTS WHERE ATROPHY DEVELOPED IN BOTH KIDNEYS.

REGARDING THE ROLE OF TREATMENT CHOICE

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BASED ON THE PATIENT'S EXISTING CONDITION AND COMORBIDITIES, OPEN SURGICAL REVASCULARIZATION AS IDENTIFIED BY MARONE AND CAMBRIA IDENTIFIED REVASCULARIZATION AS CLINICALLY BENEFICIAL IN THOSE PATIENTS WITH RAPID DECLINE IN EXCRETORY RENAL FUNCTION, AND ALSO THOSE PATIENTS WITH A DUPLEX ULTRASOUND THAT IDENTIFIED NORMAL RENAL RESISTIVE INDICES, AND I'LL SPEAK ABOUT THAT AGAIN IN A SECOND. THESE WERE LONG-TERM CLINICAL MARKERS OF SUCCESS IN THIS RETROSPECTIVE REVIEW OF 235 PATIENTS PERFORMED AT THE MASSACHUSETTS GENERAL HOSPITAL.

REGARDING DISCUSSION QUESTION 2, THE USE OF INTERMEDIATE OR SURROGATE OUTCOMES SUCH AS BLOOD PRESSURE IMPROVEMENT WITH NUMBER OF MEDICATIONS VERSUS HARD HEALTH OUTCOMES SUCH AS MORTALITY, DECREASED MI AND STROKE, SVS BELIEVES THAT BOTH OF THESE FORMS OF OUTCOMES ARE INEXTRICABLY LINKED. YOU'VE SEEN ALL THOSE DATA ALREADY PRESENTED AND THEY'RE BOTH IMPORTANT MEASURES.

WITH REGARD TO THE CURRENT STATE OF PRIMARY SURGICAL DIRECTION IN RENAL ARTERY RECONSTRUCTION FOLLOWING STENTING, THE DATA ARE SUBSTANTIAL IN TERMS OF THE PERIOPERATIVE DEATH RATE. PERIOPERATIVE DEATH RATE FOR OPEN RENAL ARTERY REVASCULARIZATIONS IS IN THE THREE TO SIX PERCENT

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RANGE, ALTHOUGH OFTENTIMES THESE DEATHS OCCURRED IN PATIENTS UNDERGOING SIMULTANEOUS AORTIC AND/OR OTHER REVASCULARIZATION PROCEDURES, OR THEY OCCURRED IN PATIENTS WITH EXTREMELY DIFFUSE ATHEROSCLEROSIS. AS SEEN FROM THE PREVIOUS PRESENTERS, THE PERIPROCEDURAL DEATH RATE FOR RENAL STENTING IS SUBSTANTIALLY LESS, PERHAPS A THIRD TO A HALF OF THAT OF THE SURGICAL TREATMENT OPTION.

NUMBER TWO --

DR. GARBER: DR. ZWOLAK, I'M SORRY, I'M GOING TO HAVE TO ASK YOU TO STOP. YOUR TIME'S UP.

DR. ZWOLAK: OKAY. THANKS VERY MUCH.

DR. GARBER: THANK YOU. DR. KELLEY, TO BE FOLLOWED BY DR. MURPHY.

DR. KELLEY: GOOD MORNING. THANK YOU FOR THE OPPORTUNITY AND ALLOWING ME TO PRESENT HERE. AS THE SOLE REPRESENTATIVE I THINK FROM INDUSTRY, IT SPEAKS TO THE DIFFICULTY IN PLAYING TO THIS ENVIRONMENT, AND I WAS A LITTLE SURPRISED TO SEE THAT IN THE LISTING THIS MORNING. SO THIS IS, I'M A VASCULAR SURGEON WHO IS PRESENTLY THE MEDICAL DIRECTOR FOR ALL THE PERIPHERAL PRODUCTS AT BOSTON SCIENTIFIC. FORTUNATELY, I ACTUALLY TRAINED UNDER BOB ZWOLAK, SO I CAN ATTEST TO HIS SKILL IN OPEN PROCEDURES, AND IT IS REMARKABLE FOR ME TO HEAR HIM

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SAY THAT RENAL ARTERY STENTING ACTUALLY HAS A VERY STRONG PLACE IN PATIENT CARE.
QUICK OBJECTIVES, I'LL GO THROUGH THIS QUICKLY SO WE CAN MOVE FORWARD, AND SIX MINUTES GOES BY QUICKLY. OUR OBJECTIVE HERE IS TO SUPPORT MAINTENANCE OF COVERAGE OR CURRENT MEDICARE COVERAGE FOR RENAL ARTERY STENTING. I'M GOING TO PROVIDE YOU SOME OF THE RENAISSANCE CLINICAL DATA THAT IS AVAILABLE NOW OUT TO TWO YEARS FOR RENAL ARTERY STENTING IN PATIENTS, AND THEN ALSO TOUCH UPON SOME OF THE CORAL TRIAL. AS YOU'VE HEARD FROM DR. COOPER, AND I'M VERY ENCOURAGED TO SEE AN UP RAMP IN THE ENROLLMENT FOR CORAL, BECAUSE I THINK FROM A SCIENTIFIC POINT OF VIEW IT IS THE RIGHT STUDY TO DO. I THINK FROM AN INDUSTRY PERSPECTIVE IT'S A VERY CHALLENGING STUDY TYPE TO DO, AND IT PRESENTS SOME ETHICAL CHALLENGES IN TERMS OF ENROLLMENT.
JUST SO YOU'RE AWARE, THE CORAL TRIAL IS THE ONLY RENAL ARTERY STENTING TRIAL THAT'S GOING ON IN THE UNITED STATES. THERE'S NO INDUSTRY-SPONSORED TRIAL GOING ON AT THIS TIME, SO CORAL IS IT. SO IF MEDICARE COVERAGE IS LIMITED TO PARTICIPATION IN CLINICAL TRIALS, YOU'RE GOING TO LIMIT PATIENTS TO BE REQUIRED TO BE IN A RANDOMIZED CLINICAL TRIAL, AND THAT PUTS A CHALLENGE ON PATIENTS THEMSELVES.

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I'M NOT GOING TO GO THROUGH THIS. SUFFICE IT TO SAY THAT THE VARIOUS CLINICAL ORGANIZATIONS HAVE ALL COME OUT IN SUPPORT OF RENAL ARTERY STENTING. THE BIASES ARE DIFFERENT. CLEARLY I WAS A VASCULAR SURGEON WHO HAD AN ACADEMIC PRACTICE WHO DID RENAL ARTERY BYPASS, RENAL ARTERY STENTING, AND HAD A VERY LARGE DIALYSIS PRACTICE. AND I CAN TELL YOU, THE PASSION FOR RENAL ARTERY STENTING COMES FROM THE DESIRE TO PREVENT DIALYSIS IN A MAJORITY OF PEOPLE. THE LIFESTYLE OF A DIALYSIS PATIENT IS MISERABLE AND IF YOU CAN PREVENT THAT, THAT'S, AT LEAST FROM MY POINT OF VIEW AND MANY PHYSICIANS' POINT OF VIEW, A DESIRE TO PREVENT THAT.

NOW WE KNOW FROM THE PREVIOUS STUDIES THAT THERE'S NOT ALWAYS A CORRELATION, AND I CANNOT EMPHASIZE ENOUGH THAT WE ARE ADVOCATING FOR APPROPRIATE PATIENT SELECTION FOR RENAL ARTERY STENTING.

RENAL ARTERY STENTING IS INCREASING IN VOLUME. AS YOU CAN SEE HERE IN 2005, 35,000 RENAL ARTERY STENTING PROCEDURES.

WHAT WAS THE RENAISSANCE TRIAL? AS DR. COOPER POINTED OUT, THESE REGISTRY TYPE, REGISTRY NONRANDOMIZED TRIALS ALL HAD THEIR PROBLEMS. IT WAS A PROSPECTIVE, MULTICENTER, SINGLE-ARM TRIAL

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EVALUATING THE SAFETY AND EFFICACY OF AN EXPRESS SD STENT IN SUBJECTS WITH RENAL ARTERY STENOSIS. THE THING ABOUT THE RENAISSANCE TRIAL THAT'S DIFFERENT FROM SOME OF THE THINGS POINTED OUT IS PATIENTS HAD TO HAVE A GREATER THAN 70 PERCENT STENOSIS, PATIENTS HAD TO HAVE ALSO FAILED MEDICAL MANAGEMENT THERAPY. OUR PATIENTS ALL WERE ON ASPIRIN, OVER 85 PERCENT WERE ON STATIN DRUGS, AND OVER 99 OF THE HUNDRED PATIENTS WERE CONSIDERED HYPERTENSIVE AND UNCONTROLLED HYPERTENSION, ON THREE OR MORE MEDICATIONS.

WE DID, AS WAS SAID, LOOK AT A SURROGATE MARKER OF NINE-MONTH PRIMARY RESTENOSIS, WITH A PRIMARY EFFICACY ENDPOINT ALSO, LOOKING AT IF THERE WAS A WAY TO FOLLOW UP THESE PATIENTS WITH A NONINVASIVE DUPLEX STUDY. AND THESE WERE THE NINE-MONTH SIGNIFICANT OUTCOMES. WE USED AN OPC OF 40 PERCENT, WHICH WAS DERIVED FROM THE LITERATURE. MOST OF THAT LITERATURE HAS BEEN PRESENTED TO YOU TODAY. THE EXPRESS SP CAME IN AT 21.3 PERCENT, STATISTICALLY SIGNIFICANT.

IN ADDITION, WE ALSO SHOWED CONCORDANCE BETWEEN DUPLEX ULTRASOUND AND ANGIOGRAPHY. WE DID HAVE HYPERTENSION, IMPROVEMENT IN SYSTOLIC HYPERTENSION, AND I'LL GO THROUGH THAT BRIEFLY HERE.

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WE DO NOT SEE ANY CHANGE WITH DIASTOLIC FUNCTION. WE ALSO HAD MAINTENANCE OF SERUM CREATININE LEVELS, AND NO PATIENT IN THE ENTIRE STUDY WENT ON TO REQUIRE RENAL REPLACEMENT THERAPY TO TWO YEARS, DESPITE THE FACT THAT THESE ARE PATIENTS WHO HAD ALL FAILED MEDICAL MANAGEMENT.

LOW RATE OF MAJOR ADVERSE EVENTS. AS YOU CAN SEE, MOST OF THE ADVERSE EVENTS WERE TARGETED TO LEAD TO REVASCULARIZATION, MOST OF THOSE WERE DUPLEX TRIGGERED AS THE PROTOCOL STATEMENT.

SO IN CONCLUSION, RENAL ARTERY STENTING WITH THE EXPRESS SD STENT SUCCESSFULLY TREATS OSTIAL RENAL ARTERY STENOSIS, IT DEMONSTRATED STABILIZATION OF HYPERTENSION, AND A FREEDOM FROM RENAL REPLACEMENT THERAPY FOR TWO YEARS. WE HOPE AND NEED -- WE HAVE GONE THROUGH THE PMA SUBMISSION PROCESS. HE HOPE THAT WE WILL HAVE A PMA APPROVAL TO ALLOW THE U.S. MARKET TO HAVE A PURPOSE-FILLED RENAL STENT AVAILABLE TO YOU THAT IS FDA-APPROVED, WHICH CURRENTLY DOES NOT EXIST AT THIS TIME.

SO IN CONCLUSION, CONTINUED COVERAGE FOR RENAL ARTERY STENTING FOR INDICATED PATIENTS IS REASONABLE AND NECESSARY. THE CURRENT PRACTICE, AVAILABLE DATA, AND SOCIETY GUIDELINES IS CONSISTENT SPECIALTIES AND SUPPORTS MAINTENANCE OF ONGOING

COVERAGE. WHILE CORAL IS VERY IMPORTANT AND SHOULD BE ALLOWED TO CONTINUE, THE RESTRICTION OF RENAL ARTERY STENTING TO PATIENTS ENROLLED IN THE ONLY RENAL ARTERY STENTING TRIAL IN THE UNITED STATES HAS ETHICAL CONSIDERATIONS WHEN YOU'RE RESTRICTING APPLICATIONS, AND OUR RECOMMENDATION IS TO MAINTAIN CURRENT COVERAGE FOR RENAL ARTERY STENTING. THANK YOU VERY MUCH FOR YOUR TIME.

DR. GARBER: THANK YOU. DR. MURPHY.

DR. MURPHY: GOOD MORNING, AND THANK YOU FOR THE OPPORTUNITY TO ADDRESS YOU TODAY. I'M TIM MURPHY, I'M AN INTERVENTIONAL RADIOLOGIST AT RHODE ISLAND HOSPITAL IN PROVIDENCE, AND A PROFESSOR OF RADIOLOGY AT BROWN MEDICAL SCHOOL. I'M SPEAKING TO YOU TODAY ON BEHALF OF THE SOCIETY OF INTERVENTIONAL RADIOLOGY. SIR IS A 5,000-MEMBER ORGANIZATION OF INTERVENTIONAL RADIOLOGISTS, A SPECIALTY THAT DESCRIBED CATHETER-BASED DIAGNOSTIC PROCEDURES, ANGIOPLASTY AND STENT PLACEMENT IN THE 1950S AND THE 1960S.

I HAVE A NUMBER OF DISCLOSURES. I'M CURRENTLY SERVING AS CO-PI OF THE CORAL STUDY. THE SOCIETY, OF COURSE, RECEIVES A TREMENDOUS AMOUNT OF INDUSTRY SUPPORT. I HAVE RECEIVED RESEARCH GRANTS FROM THE NATIONAL HEART, LUNG AND BLOOD INSTITUTE,

AND SUPPLEMENTS FOR NIH STUDIES FROM A NUMBER OF INDUSTRY PARTNERS INCLUDING BOSTON SCIENTIFIC, CORDIS, GUIDANT AND OTSUKA PHARMACEUTICALS. BUT I DON'T RECEIVE RESEARCH EDUCATION HONORARIA FOR ADVISORY PANELS, ET CETERA, ET CETERA, AND I'M NOT BEING PAID TO SPEAK WITH YOU TODAY, I PAID FOR MY OWN WAY HERE.

I'M GOING TO SKIP OVER THE REVIEW BECAUSE IT'S BEEN COVERED IN A LOT OF DETAIL. I THINK EVERYBODY APPRECIATES THAT THE NUMBER OF STUDIES THAT HAVE BEEN DONE SO FAR LOOKING AT RENAL ARTERY INTERVENTIONAL PROCEDURES IS SMALL AND THERE ARE A NUMBER OF METHODOLOGICAL FLAWS, AND IT'S HARD TO DRAW CONCLUSIONS. THE STUDIES SEEM TO SHOW LITTLE BENEFIT OF STENTING OR ANGIOPLASTY, OR LITTLE BENEFIT, BUT I BELIEVE THAT THOSE STUDIES ARE REALLY SO PROFOUNDLY METHODOLOGICALLY FLAWED THAT THEIR CREDIBILITY IS SEVERELY UNDERMINED. I WOULD SAY AT THIS POINT WE'RE IN A PERIOD OF NOT HAVING A LOT OF EVIDENCE.

WE HEARD ABOUT THE GROWTH AND NOW IT HAS BEEN EXTRAPOLATED OUT TO 2005 WITH A CONTINUING FAIRLY STEEP UP-CURVE, AND I THINK THAT GIVES EVERYBODY A LOT OF CONCERN, PHYSICIANS AND PATIENTS ALIKE.

AS FAR AS WHAT WE KNOW CURRENTLY, THE

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STUDIES THAT WE HAVE ARE FEW IN NUMBER AND FLAWED.
WE NEED DATA. THE CORAL STUDY IS A KEY STUDY TO HELP
PROVIDE THAT.
IN THE BIGGEST MEDICAL THERAPY, THE
BIGGEST STUDY COMPARING MEDICAL THERAPY AND
ANGIOPLASTY, AGAIN, WE HEARD THAT STENTING WASN'T
USED, DRUG THERAPY WAS RESTRICTED FOR THE STENT
ANGIOPLASTY GROUP, AND 44 PERCENT OF PATIENTS CROSSED
OVER FROM MEDICAL TO ANGIOPLASTY AND STILL WERE
ANALYZED ACCORDING TO INTENTION TO TREAT AS PART OF
THE MEDICAL GROUP.
HOWEVER, AGAIN, POINTING OUT SOME OF THE
METHODOLOGIC FLAWS OF SOME OF THESE STUDIES, IN THIS
BIGGEST STUDY, RANDOMIZED TRIAL, WE NOTE FROM THE
AUTHORS' MANUSCRIPT THAT PATIENTS ARE MORE LIKELY TO
HAVE IMPROVEMENT IN THEIR BLOOD PRESSURE CONTROL WHEN
THEY WERE TREATED WITH ANGIOPLASTY, MORE LIKELY TO BE
CURED, AND LESS LIKELY TO HAVE WORSENING OF EITHER
BLOOD PRESSURE CONTROL OR PROGRESSION TO RENAL ARTERY
CONCLUSION. SO THERE ARE DATA IN THOSE STUDIES THAT
SUGGEST HOW RENAL ARTERY INTERVENTIONS ARE
BENEFICIAL, AND I THINK MOST OF US IN CLINICAL
PRACTICE HAVE CLEARLY SEEN PATIENTS WHO HAVE
BENEFITED FROM THE PROCEDURE.
THESE ARE THE COVERAGE ISSUES THAT I'D

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LIKE TO ADDRESS IN THE NEXT COUPLE OF MINUTES. THE ISSUE OF ANGIOPLASTY AND/OR STENTING, WHEN IS IT APPROPRIATE TO HAVE BOTH OF THOSE CODES, IF EVER. INITIAL MANAGEMENT USING ANGIOPLASTY OR STENTING, OR SHOULD PEOPLE UNDERGO MEDICAL MANAGEMENT.
I'D LIKE TO DISCUSS SOME OF THE DOUBTERS TO CLINICAL TRIAL FOR A MOMENT, THE ISSUE OF DISTAL INVOLVED PROTECTION, IS IT NECESSARY, AND THEN THE ISSUE OF PROPHYLACTIC PTRAS, OR RENAL ANGIOPLASTY STENT PLACEMENT FOR RENAL PRESERVATION.
FIRSTLY, SIR DEVELOPED THE CODES FOR BOTH RENAL ANGIOPLASTY AND PERIPHERAL STENT PLACEMENT. WHEN THEY WERE FIRST IMPROVED BY A CPT EDITORIAL COMMITTEE IN 1992, IT WAS NEVER THE INTENTION THAT THEY WOULD BOTH BE USED TOGETHER. SIR RECOMMENDS THAT PROVIDERS BE REIMBURSED FOR EITHER RENAL ANGIOPLASTY IF NO STENT IS PLACED, OR THE RENAL CODE IF THE STENT IS PLACED, BUT NOT BOTH, AS WE HAVE SEEN IS OFTEN THE PRACTICE FOR THE SAME PATIENT ON THE SAME DAY OF SERVICE.
AT WHAT TIME DURING THE PATIENT'S DISEASE HISTORY IS RENAL ANGIOPLASTY OR STENT PLACEMENT INDICATED? GIVEN THE CURRENT KNOWLEDGE BASE, WE BELIEVE THAT RENAL ARTERY REVASCULARIZATION IS RARELY INDICATED AS THE DE NOVO TREATMENT FOR RENAL ARTERY

STENOSIS AND CLINICAL SEQUELA. PATIENTS SHOULD UNDERGO A DEDICATED, SYSTEMATIC TRIAL OF MEDICAL MANAGEMENT BY A MEDICAL SPECIALIST FOLLOWING PUBLISHED GUIDELINES PRIOR TO REFERRAL FOR INTERVENTIONS. THAT GOES ALONG WITH THE PRINCIPLE OF FIRST DO NO HARM, AND MEDICAL MANAGEMENT OBVIOUSLY IS LOWER RISK THAN INTERVENTION, SO MEDICAL MANAGEMENT SHOULD HAVE A TRIAL FIRST.

WE'VE HEARD A LITTLE BIT ABOUT THE IMPORTANCE OF THE CORAL STUDY AND HOW IT IS A METHODOLOGICALLY SOUND, WELL FUNDED NIH STUDY THAT WILL BE DEFINITIVE IN PROVIDING ANSWERS FOR THIS DISEASE, ANSWERS THAT WE SORELY LACK. WE NOTE THAT THERE ARE ECONOMIC DISINCENTIVES TO INVESTIGATIVE PARTICIPATION AND ENROLLMENT IN THE U.S. HAS BEEN LACKLUSTER ALMOST UNIVERSALLY ACROSS THE BOARD, PARTICULARLY IN STUDIES THAT COMPARE CONSERVATIVE VERSUS INVASIVE MANAGEMENT. AND WE IMPLORE MEDICARE TO COME UP WITH A PROGRAM THAT WILL AT LEAST ELIMINATE OR BLUNT THESE ECONOMIC DISINCENTIVES TO GETTING THE ANSWERS THAT WILL FORM SOUND COVERAGE DECISIONS.

DISTAL PROTECTION, THERE'S LITTLE EVIDENCE OF THE BENEFIT OF DISTAL PROTECTION. WE DON'T BELIEVE THAT DISTAL PROTECTION SHOULD BE REQUIRED FOR

REIMBURSEMENT. SEPARATE PROFESSIONAL REIMBURSEMENT IF USED IS NOT SUPPORTED AT THIS TIME, THERE'S JUST SIMPLY NO EVIDENCE TO SHOW THAT IT DOES ANY MORE BENEFIT THAN HARM.

FINALLY TO ADDRESS PROPHYLACTIC PTRAS, AGAIN, GETTING BACK TO THE NEED FOR CLINICAL MANIFESTATIONS OF THE DISEASE, WE BELIEVE THAT RENAL ARTERY STENOSIS WITHOUT REFRACTORY HYPERTENSION OR CHRONIC KIDNEY DISEASE SHOULD NOT BE AN INDICATION FOR REVASCULARIZATION OF THE KIDNEY ARTERIES. THANK YOU.

DR. GARBER: THANK YOU VERY MUCH.

IMPRESSIVE TIMING THERE.

ALL RIGHT. WE NOW HAVE THREE OPEN PUBLIC SPEAKERS WHO HAVE SIGNED UP TO SPEAK. LET ME ALSO THANK ALL OF THE SCHEDULED SPEAKERS, AND I HOPE THAT YOU WILL ALL STICK AROUND AFTER LUNCH, BECAUSE I'M SURE THE PANEL WILL HAVE A NUMBER OF QUESTIONS FOR YOU AT THAT TIME.

SO WE WILL BEGIN WITH DR. CAMBRIA -- YOU HAVE THREE MINUTES EACH. HE WILL BE FOLLOWED BY DR. ROSENFIELD, THEN DR. GERHARD-HERMAN.

DR. CAMBRIA: THANK YOU, MR. CHAIRMAN. MY NAME IS RICHARD CAMBRIA, I'M A PROFESSOR OF SURGERY AT THE HARVARD MEDICAL SCHOOL AND CHIEF OF THE

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DIVISION OF VASCULAR AND ENDOVASCULAR SURGERY AT THE MASSACHUSETTS GENERAL HOSPITAL IN BOSTON. I'VE BEEN LECTURING ABOUT OR WRITING ABOUT THIS DISEASE PROCESS FOR OVER 20 YEARS ON A CIRCUIT THAT HAS OFTEN INCLUDED MANY OF THE SPEAKERS THAT YOU HAVE HEARD THIS MORNING. MY OWN PERSPECTIVE IS THAT OF A VASCULAR SURGEON. I AM HERE ON BEHALF OF THE SOCIETY FOR VASCULAR SURGERY, WHO I CERTAINLY HOPE WILL REIMBURSE MY TRAVEL EXPENSES.

I AGREE WITH MUCH THAT HAS BEEN SAID BY MY PREDECESSORS. AS A VASCULAR SURGEON, I HAVE PERFORMED MANY, MANY OPEN SURGICAL REPAIRS OF RENAL ARTERY LESIONS AND I HAVE PERSONALLY LOOKED INTO THE INSIDE OF LITERALLY THOUSANDS OF RENAL ARTERY OSTIA. THERE IS NO QUESTION THAT EVEN VASCULAR SURGEONS HAVE ACCEPTED THE MIGRATION OF THE PRIMARY FORM OF INTERVENTIONAL THERAPY FROM OPEN SURGERY TO RENAL ARTERY STENTING, AND THIS IS FOR THE VERY OBVIOUS REASONS OF THE SIGNIFICANT DIFFERENCE IN THE MORBIDITY OF THE TWO PROCEDURES.

THAT BEING SAID, I CERTAINLY AGREE THAT IT IS ILLOGICAL AND IRRELEVANT TO USE THE ANALOGY WITH CAROTID ANGIOPLASTY AND STENTING AND OPEN CAROTID SURGERY. THE TWO ARE FUNDAMENTALLY DIFFERENT DISEASE PROCESSES AND THE SURGICAL INTERVENTION IN TERMS OF

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MORBIDITY ARE VASTLY DIFFERENT.
WE HAVE BEEN TEACHING OUR VASCULAR SURGERY TRAINEES SINCE THE INCEPTION OF OUR SPECIALTY EXAMINATIONS THAT THE APPROPRIATE POSTURE TOWARDS A "ASYMPTOMATIC RENAL ARTERY LESION," THAT IS, ONE IN THE ABSENCE OF HYPERTENSION OR ANY EVIDENCE OF ISCHEMIC NEPHROPATHY, SHOULD BE CONSERVATIVE. THAT REMAINS THE APPROPRIATE ANSWER WHEN WE EXAMINE OUR FELLOWSHIP APPLICANTS EVEN TODAY.
YES, THERE CLEARLY ARE PATIENTS WHO DO BENEFIT, EVEN DRAMATICALLY, FROM RENAL ARTERY INTERVENTION. AND OUR OWN EFFORTS AND PUBLICATIONS OVER THE PAST 20 YEARS HAVE FOCUSED ON THE PREDICTION OF THE FUNCTIONAL RESPONSE TO REVASCULARIZATION. I CAN TELL YOU THAT PERSONALLY I HAVE PERFORMED NO MORE GRATIFYING VASCULAR INTERVENTION THAN TO RETRIEVE A PATIENT FROM RENAL REPLACEMENT THERAPY. THESE PATIENTS ARE NOT COMMON BUT THEY DO REPRESENT THE DRAMATIC FAR END OF THE SPECTRUM OF THE BENEFIT OF RENAL ARTERY INTERVENTIONS.
THE PROBLEM OF COURSE IS THE LARGE MASS OF PATIENTS WHO, AS YOU HAVE HEARD, ARE INCREASINGLY BEING OFFERED RENAL ARTERY INTERVENTIONS WITH VERY SOFT INDICATIONS. I APPRECIATE THE AGENCY'S DILEMMA IN THIS REGARD. HOWEVER, I WOULD LIKE TO CLOSE BY

STATING THAT THERE ARE DISTINCT PATIENT AND ANATOMIC SUBSETS WHEREIN THE BENEFITS OF INTERVENTION BASED ON AVAILABLE EVIDENCE, ALBEIT NOT LEVEL I, IS CLEAR. I WOULD PARENTHETICALLY ADD THAT THERE ARE ADDITIONAL CIRCUMSTANCES AS VASCULAR INTERVENTIONS EVOLVE, AND I WOULD USE THE EXAMPLE OF CONCOMITANT RENOVASCULAR DISEASE IN PATIENTS BEING TREATED WITH AORTIC PATHOLOGY. THESE DAYS THE PRESENCE OF EVEN AN ASYMPTOMATIC RENAL ARTERY STENOSIS MAY BENEFIT FROM STENTING IN THE CONTEXT OF AN OTHERWISE INVASIVE PROCEDURE FOR AORTIC PATHOLOGY, MOST NOTICEABLY STENT GRAFT REPAIR OF ABDOMINAL AORTIC ANEURYSM. I THANK YOU FOR YOUR ATTENTION.

DR. GARBER: THANK YOU, DR. CAMBRIA.

NEXT, DR. ROSENFIELD.

DR. ROSENFIELD: MR. CHAIRMAN AND PANELISTS, THANK YOU FOR THE PRIVILEGE OF SPEAKING. MY NAME IS KEN ROSENFIELD, AND I'M THE HEAD OF THE SECTION OF VASCULAR MEDICINE AND INTERVENTION AT MASS GENERAL HOSPITAL IN BOSTON. YOU'RE GETTING A LOT OF US TODAY. MY TRAVEL HERE WAS SUPPORTED BY THE SCA&I. RELEVANT CONFLICTS ARE OUTLINED IN YOUR PAMPHLETS, AND THESE INCLUDE THE FACT THAT I AND MY INSTITUTION HAVE RECEIVED RESEARCH AND/OR EDUCATIONAL GRANTS FROM VARIOUS INDUSTRY SPONSORS, AND I HAVE SERVED AS A

PAID ADVISOR OR CONSULTANT TO SEVERAL COMPANIES. I'M A CLINICIAN THAT HAS BEEN INVOLVED IN CARING FOR PATIENTS WITH RENOVASCULAR DISEASE FOR 20 YEARS. I CURRENTLY SERVE AS CHAIRPERSON OF THE AHA CARDIOVASCULAR CATHETERIZATION COMMITTEE, THE PRIOR CHAIR OF THE PERIPHERAL VASCULAR DISEASE COMMITTEE OF THE ACC, AND THE CURRENT CHAIR OF THE PVD COMMITTEE FOR THE SCA&I. I WAS THE NATIONAL PI OF THE ASPIRE II TRIAL, WHICH WAS THE FIRST STUDY THAT OBTAINED FDA APPROVAL FOR RENAL STENT DEPLOYMENT IN THE UNITED STATES, AND I'VE ALSO BEEN INVOLVED IN THE CORAL TRIAL FROM ITS OUTSET, SERVING AS THE CHAIRMAN OF THE CORAL SITE SELECTION COMMITTEE.

I WOULD LIKE TO SPECIFICALLY NOTE THAT I AM HERE TODAY SPEAKING ON BEHALF OF SCA&I AND ITS NEARLY 4,000 MEMBER CLINICIANS WHO CARE FOR PATIENTS WITH CARDIOVASCULAR AND VASCULAR DISEASE. FIRST, MY COLLEAGUES IN THE SCA&I WOULD LIKE TO EMPHASIZE THAT WE SUPPORT THE ACCRUAL OF ADDITIONAL EVIDENCE TO REFINE PATIENT SELECTION FOR RENAL ANGIOPLASTY AND STENTING, AND WE SUPPORT THE CORAL TRIAL. WHILE THIS IS OUR POSITION, THE SCA&I DOES NOT BELIEVE THAT EVIDENCE DEVELOPMENT SHOULD OCCUR AT THE COST OF RESTRICTING ACCESS TO IMPORTANT THERAPIES THAT CAN REDUCE MORBIDITY OR MORTALITY IN A GIVEN PATIENT.

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CARE SHOULD BE TAKEN NOT TO THROW OUT THE BABY WITH THE BATH WATER.

WE DO NEED MORE INFORMATION AS TO WHICH PATIENTS ARE MORE OR LESS LIKELY TO BENEFIT FROM THIS THERAPY. HOWEVER, LIMITING COVERAGE TO PATIENTS ENROLLED IN THE CORAL OR OTHER TRIAL WOULD BE A DISSERVICE TO THE MEDICARE BENEFICIARIES IN THE 21 STATES, FOR EXAMPLE, WHERE THERE ARE NO CORAL SITES, AND FOR MANY PATIENTS WHO ARE NOT ELIGIBLE FOR ENROLLMENT. MEDICARE AND OTHER PATIENTS WHO STAND TO BENEFIT FROM AND CURRENTLY HAVE ACCESS TO RENAL REVASCULARIZATION BY STENTING CANNOT BE RELEGATED SOLELY TO MEDICAL THERAPY OR TO HIGHER RISK SURGICAL REVASCULARIZATION.

WHILE MOST HAVE TODAY FOCUSED ON EVIDENCE FOR OR AGAINST RENAL STENTING, EVIDENCE SUPPORTING MEDICAL THERAPY FOR THIS DISEASE IS NO MORE ROBUST AND MAY BE LESS SO THAN THAT FOR OPENING THE NARROW VESSEL. LIKEWISE THE COST, BOTH FINANCIAL AND LIFESTYLE, OF PROLONGED LIFETIME ADMINISTRATION OF MEDICATIONS CAN EXCEED THAT OF REVASCULARIZATION.

IT IS IMPORTANT TO POINT OUT THAT WHILE HAVING A ROBUST EVIDENCE BASE IS ALWAYS DESIRABLE, ABSENCE OF A CONCLUSIVE EVIDENCE BASE DOES NOT MEAN THAT A THERAPY IS INEFFECTIVE AND SHOULD NOT BE

APPLIED. MOST OF THE DECISIONS, INDEED, THAT WE MAKE IN CARING FOR OUR PATIENTS ARE MADE WITHOUT THE BENEFIT OF A CONCLUSIVE BODY OF DATA. WERE LEVEL I OR IIA EVIDENCE TO BE REQUIRED FOR ALL DECISIONS WE MAKE, WE WOULD ALL BE PARALYZED AS CLINICIANS. WE AS CLINICIANS MUST TAKE INTO ACCOUNT THE WEIGHT OF THAT EVIDENCE AS IT PERTAINS TO THE INDIVIDUAL PATIENT WHO IS BEFORE US.

I SERVED ON THE ACC/AHA/SVS/SVMB GUIDELINES DOCUMENT WRITING GROUP WHICH YOU'VE HEARD ABOUT. THE ASSIGNMENT TO CLASS IIB FOR CERTAIN INDICATIONS FOR RENAL STENTING BY A GROUP OF EXPERTS WAS NOT INTENDED TO RESTRICT ACCESS, BUT RATHER TO INFORM PHYSICIANS AND THEIR PATIENTS THAT THESE PARTICULAR INDICATIONS WERE ONES FOR WHICH THERE WAS AN EVOLVING AND SOMETIMES CONFLICTING EVIDENCE BASE, AND THAT CLINICIANS SHOULD FACTOR THAT IN WHEN DECIDING UPON THERAPY FOR AN INDIVIDUAL PATIENT. THAT DESIGNATION WAS INTENDED TO LEAVE THE ULTIMATE DECISION-MAKING IN THE HANDS OF A PATIENT AND HIS OR HER CAPABLE AND COMPETENT PHYSICIAN.

DR. GARBER: DR. ROSENFIELD, I'M SORRY, BUT YOUR TIME IS UP.

DR. ROSENFIELD: THANK YOU.

DR. GARBER: DR. GERHARD-HERMAN.

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DR. GERHARD-HERMAN: THANK YOU FOR THE OPPORTUNITY TO SPEAK. I'M THE CURRENT CHAIR OF THE ACC PVD COMMITTEE AND I'M A NONINTERVENTIONAL CARDIOLOGIST.

THE TWO POINTS THAT WE WANTED TO RAISE FROM THE PERSPECTIVE OF OUR GROUP IN THE AMERICAN COLLEGE OF CARDIOLOGY, ONE IS THAT THERE ARE SUBPOPULATIONS OF PATIENTS WHERE THERE IS CLEAR BENEFIT TO INTERVENTION IN THE SETTING OF RENAL ARTERY STENOSIS. THAT'S ALREADY BEEN DISCUSSED BUT WE JUST WANTED TO SAY IT AGAIN. THOSE ARE THE PATIENTS WITH BILATERAL RENAL ARTERY STENOSIS AND RENAL ARTERY STENOSIS IN THE SETTING OF A SOLITARY KIDNEY.

BUT IT HAS ALREADY BEEN DISCUSSED THAT THERE'S A HUGE NUMBER OF PATIENTS WHO HAVE RENAL ARTERY STENOSIS THAT DON'T FIT IN THOSE CATEGORIES, AND WE WOULD SAY WE HAVE INSUFFICIENT EVIDENCE TO DECIDE WHAT TO DO WITH THOSE PATIENTS. AND I THINK AT THIS POINT WE ALL STAND TOGETHER IN CONTINUING TO SUPPORT THE ACC AND AHA GUIDELINES FOR BOTH LEVEL I AND LEVEL II RECOMMENDATIONS IN TERMS OF TREATMENT OF RENAL ARTERY STENOSIS, AND WE ENCOURAGE CONTINUED SUPPORT OF THE CLINICAL TRIALS.

AND THE LAST POINT IS THAT WHILE WE

ENCOURAGE SUPPORT OF ENROLLMENT IN THE CORAL TRIAL, THERE ARE A LOT OF PATIENTS WHO WON'T HAVE ACCESS TO A CORAL SITE THAT WE TOO DO NOT WISH TO DEPRIVE FROM RENAL INTERVENTION. THANK YOU.

DR. GARBER: THANK YOU VERY MUCH. WE HAVE A GUEST HERE WHO I WONDER IF WE COULD ASK TO JUST MAKE A FEW BRIEF COMMENTS, AND THAT'S DR. KENT CAVANAUGH FROM THE FDA, WHO WASN'T REALLY PREPARED TO SPEAK TODAY. I'D ASK HIM IF HE COULD JUST MENTION THE CURRENT STATUS OF FDA APPROVAL FOR DEVICES USED TO STENT RENAL ARTERIES.

DR. CAVANAUGH: SURE, THANK YOU, AND I WILL BE BRIEF SO WE CAN HAVE ABOUT 35 MINUTES FOR LUNCH TODAY.

MY NAME IS KENT CAVANAUGH, I'M A SCIENTIFIC REVIEWER WITHIN THE DIVISION OF CARDIOVASCULAR DEVICES AT THE FOOD AND DRUG ADMINISTRATION. I'D JUST LIKE TO PROVIDE A BRIEF REGULATORY OVERVIEW OF RENAL ARTERY STENTING FROM OUR PERSPECTIVE.

IN OUR REGULATORY CLASSIFICATION SCHEME WE CONSIDER RENAL ARTERY STENTS TO BE CLASS III DEVICES FOR WHICH A PREMARKET APPROVAL APPLICATION IS APPROPRIATE. TO SUPPORT THAT TYPE OF APPLICATION, THE DEVICE NEEDS TO HAVE REASONABLE ASSURANCE OF

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SAFETY AND EFFECTIVENESS FOR ITS INTENDED USE PRIOR TO APPROVAL OF THAT MARKETING APPLICATION. TO DATE THERE HAVE BEEN TWO PMAS APPROVED FOR RENAL ARTERY STENTS FOR ANY INDICATION, ONE IN 2002 AND ONE IN 2003, I BELIEVE. THE APPROVED INDICATIONS FOR BOTH DEVICES ARE SIMILAR AND THAT IS, THEY ARE INDICATED FOR USE FOLLOWING FAILED OR SUBOPTIMAL PERCUTANEOUS TRANSLUMINAL RENAL ANGIOPLASTY, BALLOON ANGIOPLASTY, AS DEFINED BY CERTAIN LESION AND HEMODYNAMIC CHARACTERISTICS. THERE ARE NO STENTS APPROVED SO FAR TO TREAT RENAL ARTERY STENOSIS AS A PRIMARY TREATMENT OPTION. BY THE SAME TOKEN, WHILE INVOLVED PROTECTION DEVICES ARE REGULATED SOMEWHAT DIFFERENTLY, THERE ARE NONE CURRENTLY MARKETED WITH A RENAL ARTERY INDICATION, THEY ARE ONLY MARKETED WITH INDICATIONS FOR USE IN CAROTID ARTERIES AND BYPASS GRAFTS. THAT BEING SAID, WHILE I WON'T GET INTO RECOMMENDATIONS FOR STUDY DESIGNS HERE, I WILL SAY THAT TO SUPPORT SUCH AN INDICATION LIKE THIS, FDA WOULD ENCOURAGE DEVICE MANUFACTURERS AND ACADEMIC GROUPS TO CONDUCT NEW STUDIES, GATHER ADDITIONAL CLINICAL DATA TO SUPPORT INDICATIONS LIKE THIS OR ANY INDICATION FOR WHICH -- THERE ARE NO APPROVED DEVICES, BUT FOR WHICH DEVICE USE MAY CURRENTLY

REPRESENT CLINICAL PRACTICES. THANK YOU.
DR. GARBER: THANK YOU, DR. CAVANAUGH. WE WILL TAKE OUR BREAK FOR LUNCH NOW. WE ARE RIGHT ON SCHEDULE, ACCORDING TO MY WATCH, AND WE WILL RESUME THE MEETING AT 12:05.
(LUNCH RECESS.)
DR. GARBER: SOME OF THE PRESENTERS ARE DRIFTING IN, SO ACTUALLY BEFORE WE GET STARTED WITH QUESTIONS TO THE PRESENTERS, I JUST WANTED TO SUGGEST THAT WHEN YOU LOOK AT THE QUESTIONS, I KNOW THAT NOT ALL OF YOU WERE ON THE CONFERENCE CALL ABOUT THE LOGISTICS OF THE MEETING, BUT THE INITIAL DISCUSSION QUESTIONS ARE THINGS THAT WE NEED TO KEEP IN MIND WHEN WE ANSWER THE VOTING QUESTIONS, BUT WE DON'T HAVE TO NECESSARILY GO THROUGH EACH OF THESE AS A GROUP DELIBERATING. BUT YOU ARE CERTAINLY WELCOME TO ASK OF THE PRESENTERS OR MAKE STATEMENTS ABOUT THESE QUESTIONS AT THIS POINT. IT'S INTENDED TO SORT OF SENSITIZE US TO WHAT THE ULTIMATE SCIENTIFIC AND CLINICAL ISSUES ARE WITH REGARD TO THE MAIN QUESTIONS, AS WELL AS TO THE INTERPRETATION OF THE STUDIES THAT WE'VE DISCUSSED TODAY.
DOES ANYBODY WANT TO MAKE ANY STATEMENTS THEN? AND WE CAN ASK QUESTIONS OF PRESENTERS NOW.
PRESENTERS, WHEN YOU ANSWER THE QUESTIONS, I WILL ASK

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YOU TO BE AS SUCCINCT AS POSSIBLE, BECAUSE THERE ARE MANY PEOPLE WHO BOTH MIGHT HAVE QUESTIONS OR MIGHT WANT TO ANSWER A QUESTION. WHEN YOU ANSWER A QUESTION, PLEASE COME UP TO THE MIKE THAT'S IN THE FRONT OF THE ROOM HERE ON THE STAND. ALEX.

DR. KRIST: I HAVE A QUESTION IF WE'RE GOING TO START WITH QUESTIONS CLARIFYING THINGS, AND DR. COOPER IS HERE, SO THE QUESTION IS ACTUALLY FOR YOU. I JUST WANT TO LEARN A LITTLE BIT MORE ABOUT THE CORAL STUDY, BECAUSE ONE OF THE THINGS WE'RE ASKED TO THINK ABOUT IS LIMITING COVERAGE TO PARTICIPATING IN A RESEARCH STUDY, AND I WAS HOPING YOU COULD JUST TALK A LITTLE BIT ABOUT KIND OF THE INCLUSION AND EXCLUSION CRITERIA AND, BASED ON YOUR STUDY DESIGN, WHAT TYPES OF PATIENTS WHO MIGHT HAVE AN INDICATION FOR AN INTERVENTION FOR RENAL ARTERY STENOSIS MIGHT NOT BE INCLUDED IN YOUR STUDY. THAT WOULD BE THE FIRST PART.

AND THEN THE SECOND PART I'M INTERESTED IN IS IF YOU LOOK AT SOME OF THE OTHER STUDIES LIKE IN DRASTIC, THEY QUOTED THAT 1,205 PATIENTS WERE REFERRED FOR CONSIDERATION OF INCLUSION AND THEN THAT ENDED UP WITH 106 PEOPLE BEING RANDOMIZED, SO ABOUT EIGHT PERCENT OF THOSE OR LESS THAT THEY WERE THINKING ABOUT INCLUDING WERE ACTUALLY INCLUDED. AND

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THEN YOU REPORTED TODAY THAT YOU'VE ENROLLED ABOUT 240 PATIENTS, AND I WAS JUST CURIOUS IF YOU HAD ANY TYPE OF COROLLARY NUMBER TO WHAT DRASTIC HAD AS TO HOW MANY PEOPLE MIGHT HAVE BEEN CONSIDERED OR EVALUATED TO GET THAT 240 FOR INCLUSION.

DR. GARBER: COULD I JUST ADD TO ALEX'S QUESTION, SINCE IT'S KIND OF AN EXPANSION OF ONE OF HIS POINTS, IT WOULD BE USEFUL TO KNOW WHICH PATIENT TYPES WERE EXCLUDED BECAUSE YOU AND THE OTHER INVESTIGATORS THOUGHT THAT THERE WAS SUCH COMPELLING NEED FOR STENTING THAT THEY SHOULD NOT BE RANDOMIZED.

DR. DWORKIN: I'M LANCE DWORKIN AND I'LL TAKE THAT ONE FOR CHRIS, IF YOU DON'T MIND, BECAUSE I'M THE STUDY CHAIR FOR CORAL. REGARDING WHAT TYPES OF PATIENTS WERE EXCLUDED, THE ENTRANCE CRITERIA FOR CORAL REQUIRED PATIENTS TO HAVE EITHER HYPERTENSION THAT REQUIRES TWO MEDICATIONS, OR CHRONIC KIDNEY DISEASE WITH A GFR LESS THAN 60, ARE THE MAIN INCLUSION CRITERIA, AND THEN DOCUMENTED RENAL ARTERY STENOSIS WHICH IS DETERMINED EITHER ANGIOGRAPHICALLY OR NOW NONINVASIVELY. THOSE ARE THE ONLY INCLUSION CRITERIA, SO IT'S A FAIRLY BROAD SWEEP IN TERMS OF THE POSSIBLY AFFECTED PATIENTS, AND PEOPLE DON'T HAVE TO BE HYPERTENSIVE IF THEY HAVE KIDNEY DISEASE.

IN TERMS OF EXCLUSION CRITERIA, THERE

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REALLY AREN'T THAT MANY. THERE IS A CREATININE CUTOFF OF THREE, THAT WAS SOMETHING THAT WAS DEBATED, SO PATIENTS WITH A CREATININE ABOVE THREE CAN'T ENTER. AND THAT WAS SOMETHING DEBATED, AND THE REASON THAT IT WAS SET UP THAT WAY, BECAUSE THERE WAS ACTUALLY A FEELING PRIMARILY AMONG THE INTERVENTIONALISTS, I THINK, THAT PATIENTS WITH CREATININES ABOVE THREE WERE LESS LIKELY TO BENEFIT AND, THEREFORE, THE STUDY MIGHT BE BIASED AGAINST THE INTERVENTION IF THOSE PATIENTS WERE LET IN.

YOU KNOW, IN DESIGNING THE TRIAL, I THINK WE TRIED TO BE VERY, VERY INCLUSIVE BECAUSE WE FELT THAT IN FACT THERE WERE ALMOST NO TYPES OF PATIENTS WITH RENOVASCULAR DISEASE FOR WHOM THE DATA IS CLEAR THAT ONE APPROACH OR ANOTHER IS SUPERIOR. AND IN FACT, YOU KNOW, A CRITICAL SESSION, I THINK, THAT WE HAD WAS AT ONE POINT WE WERE IN A ROOM WITH ABOUT 30 DIFFERENT PEOPLE THAT WERE INVOLVED IN DESIGNING THE TRIAL. AND I POSED THE QUESTION TO THE GROUP, DESCRIBE A SET OF CRITERIA, CLINICAL, LABORATORY OR OTHERWISE, WHERE YOU FEEL THAT IT'S DEFINITELY KNOWN THAT A PATIENT REQUIRES REVASCULARIZATION AS COMPARED TO MEDICAL THERAPY, AND THERE WAS SILENCE. SO NOBODY FELT COMFORTABLE REALLY PUTTING FORTH ANY SET OF CRITERIA FOR WHICH REVASCULARIZATION WAS REQUIRED

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AND, THEREFORE, THOSE PATIENTS SHOULDN'T BE ENROLLED IN CORAL.

SO WE HAVE PATIENTS WITH UNILATERAL AND BILATERAL DISEASE, PATIENTS WITH PRETTY SEVERE KIDNEY DYSFUNCTION, PATIENTS WITH A WHOLE VARIETY OF COMORBIDITIES, BECAUSE WE FELT AT LEAST THAT FOR MOST OF THESE CATEGORIES, THE INFORMATION WASN'T CLEAR. THE ONLY DEFINED GROUP THAT ARE SUPPOSED TO GET A STENT ARE PATIENTS THAT DEVELOP ACUTE RENAL FAILURE WHERE IT'S DOCUMENTED BY IMAGING THAT THEY HAVE GLOBAL RENAL ISCHEMIA, MEANING VERY HIGH GRADE STENOSIS, OR OCCLUSION TO ALL OF THEIR RENAL ARTERIES, AND THAT'S THE ONLY GROUP FOR WHOM THE STUDY DICTATES THAT THEY MUST BE REVASCULARIZED. OTHERWISE, THEY CAN BE RANDOMIZED.

DR. GARBER: THANK YOU.

DR. LEWIS: CAN I ASK A QUESTION REGARDING THAT AS WELL? BECAUSE THEN IT CONFLICTS WITH THE ISSUES WITH RESPECT TO THE AMERICAN HEART ASSOCIATION GUIDELINES IN TERMS OF THE CLASS I INDICATIONS FOR PEOPLE WHO HAVE FLASH PULMONARY EDEMA, UNSTABLE ANGINA. AND SO IF THAT'S THE CASE, CAN WE TRY TO RESOLVE THAT CONFLICT A LITTLE BIT AS WELL?

DR. DWORKIN: I CAN'T REALLY SPEAK TO THE GUIDELINES SPECIFICALLY, I WASN'T PARTY TO WRITING

00164

THOSE. I MEAN, I THINK IF A CLASS I, TO MY MIND ANYWAY, IF A CLASS I INDICATION MEANS THAT THERE IS PROSPECTIVE RANDOMIZED CONTROLLED TRIAL DATA THAT DOCUMENTS THAT ONE APPROACH IS SUPERIOR TO ANOTHER, I DON'T THINK THAT EXISTS FOR ALMOST ANY CLINICAL SCENARIO THAT YOU CAN DESCRIBE. I JUST DON'T THINK THE DATA ARE THAT GOOD.

AND I THOUGHT THAT THAT WAS ALSO, YOU KNOW, THE AHRQ REVIEW THAT WAS COMMISSIONED, I THOUGHT THAT WAS THEIR CONCLUSION AS WELL. I DIDN'T THINK THEY --

DR. GARBER: THAT WAS EITHER A GRADE B OR GRADE C LEVEL OF EVIDENCE, I THINK.

DR. DWORKIN: YEAH, I DON'T KNOW WHAT IT WAS. I MEAN, I PROBABLY SHOULDN'T BE TALKING TO THIS SINCE I DIDN'T WRITE THE GUIDELINES, BUT IF YOU HAVE GRADE B EVIDENCE, THEN HOW DO YOU GET TO A CLASS I INDICATION? THAT SEEMS TO ME TO BE SORT OF A METHODOLOGIC ISSUE.

DR. LEWIS: WELL, THE OTHER QUESTION IS, OR AN ADDITIONAL QUESTION IS THAT CORAL DOES EXCLUDE PEOPLE WITH HEART FAILURE AND LOW EJECTION FRACTIONS AS WELL AS --

DR. DWORKIN: IN THE REVISED PROTOCOL, THERE'S NO EXCLUSION FOR EJECTION FRACTION. THAT WAS

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SOMETHING THAT WAS PUT IN THERE INITIALLY WHICH WAS DROPPED. I MEAN, THE ONLY HEART FAILURE EXCLUSION IS IF SOMEBODY HAS BEEN ADMITTED WITHIN, I THINK IT'S THE LAST 30 DAYS, FOR CONGESTIVE HEART FAILURE. YOU KNOW, PART OF THIS IS JUST KEEPING PEOPLE OUT OF THE TRIAL THAT ARE SO ILL.

SO ONE OF THE THINGS WE WERE CONCERNED ABOUT IS THAT ACTUALLY AMONG THE COMPOSITE ENDPOINTS WHICH INCLUDES, THE PRIMARY ENDPOINT IS A COMPOSITE IN CORAL, WHICH INCLUDES, AMONG ONE OF THE ENDPOINTS IS ADMISSION TO THE HOSPITAL FOR CONGESTIVE HEART FAILURE. AND WE WERE A LITTLE BIT CONCERNED THAT THERE WERE PATIENTS WHO WERE ADMITTED VERY FREQUENTLY LIKE THAT, AND THEN IF WE ALLOWED PATIENTS LIKE THAT TO BE ENROLLED, THAT THAT PARTICULAR OUTCOME MIGHT DRIVE THE WHOLE OUTCOME OF THE TRIAL.

BUT I THINK IT'S FAIRLY STANDARD IN MANY CLINICAL TRIALS TO EXCLUDE PATIENTS THAT HAD AN MI WITHIN THE LAST 30 DAYS, OR A STROKE WITHIN A CERTAIN AMOUNT OF TIME, SO PART OF IT IS JUST THAT. YOU DON'T WANT PEOPLE THAT ARE IN THE MIDST OF AN ACUTE ILLNESS COMING INTO A LONG-TERM PROSPECTIVE TRIAL LIKE THIS WHERE YOU'RE TRYING TO LOOK AT THE IMPACT OF THESE TWO APPROACHES ON THOSE OUTCOMES. SO WE WERE TRYING TO GET A GROUP OF PATIENTS WHO AT LEAST

00166

WITH REGARD TO THE VARIOUS COMPONENTS OF THE PRIMARY ENDPOINT WERE RELATIVELY STABLE AT THE TIME THAT THEY WERE ENROLLED AND NOT ACUTELY ILL, IN THOSE CATEGORIES.

AND THAT'S REALLY THE ONLY REASON, OR THE PRIMARY REASON FOR THAT EXCLUSION. IT WASN'T THAT WE FELT THAT PATIENTS WITH HEART FAILURE WERE A GROUP FOR WHOM IT WAS CLEAR THAT ONE APPROACH WAS SUPERIOR TO THE OTHER. I DON'T THINK WE FELT THAT AT ALL.

DR. CHARYTAN: BUT THERE WAS A SECOND PART TO THE QUESTION THAT DR. KRIST HAD ASKED, AND THAT WAS HOW MANY PATIENTS WERE SCREENED TO COME UP WITH THE 200 PATIENTS THAT YOU ENDED UP WITH.

DR. DWORKIN: WE ARE KEEPING SCREENING LOGS. THE PROBLEM WITH LOOKING AT THE SCREENING LOGS LIKE THAT IS THAT WHAT PEOPLE RECORD AS A SCREENED PATIENT IS VERY VARIABLE, YOU KNOW, FROM INSTITUTION TO INSTITUTION. SO SOMETIMES A SCREENED PATIENT MIGHT BE SOMEBODY THAT HAS HYPERTENSION AND THE CREATININE OF 1.2, WHO GETS A DUPLEX ULTRASOUND ORDERED AND IT DOESN'T SHOW RENOVASCULAR DISEASE. SO THAT COULD BE A SCREENING FAILURE, BUT THAT'S NOT REALLY SOMEBODY WITH RENAL ARTERY STENOSIS OR RENOVASCULAR DISEASE WHO WAS NOT BEING ENTERED INTO THE TRIAL.

00167

AND I DON'T KNOW, CHRIS, DO WE KNOW THE PERCENTAGE OF PATIENTS THAT HAVE, ACTUALLY HAVE DOCUMENTED HIGH GRADE RENAL ARTERY STENOSIS OR STENOSIS THAT WOULD QUALIFY THEM FOR ENTRY THAT WERE BEING SCREENED AND NOT ENTERED? DO YOU HAVE A --

DR. COOPER: I'M LOOKING IT UP. I DON'T KNOW WHAT THE EXACT NUMBER IS.

DR. DWORKIN: I MEAN, CLEARLY THERE ARE PATIENTS LIKE THAT THAT ARE NOT GETTING ENTERED, AND THERE'S A VARIETY OF REASONS WHY THAT HAPPENS. PATIENTS DECLINE, YOU KNOW, AFTER THEY READ THE CONSENT FORM, OR, YOU KNOW, FOR ONE OTHER REASON OR ANOTHER. BUT I DON'T KNOW THE EXACT NUMBERS.

DR. CHARYTAN: BUT AGAIN, I THINK THAT'S PERTINENT TO THE POINT THAT IF THERE WERE ABOUT 18 OR 20,000 PROCEDURES BEING DONE BY 2000, AND I HEARD A NUMBER BEING RECENTLY MENTIONED THAT IT MIGHT BE UP TO 30,000 OR 40,000 BY 2005, THEN CLEARLY IN RESTRICTING COVERAGE TO JUST PATIENTS, A THOUSAND PATIENTS WHO ARE GOING TO BE IN THE STUDY, EVEN THOUGH MANY PATIENTS MAY BE GETTING PROCEDURES, THAT WOULD BE EXCLUDING POTENTIALLY A SIGNIFICANT NUMBER OF PATIENTS WHO MIGHT CONCEIVABLY BENEFIT. AND I THINK ONE COULD ARGUE THAT THERE IS A PROBLEM WITH THAT APPROACH.

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DR. DWORKIN: YEAH. I DON'T DISAGREE WITH THAT. I MEAN, I CAN'T REALLY SPEAK FOR CORAL AS A STUDY BECAUSE WE'RE A GROUP OF INDIVIDUALS, BUT I DON'T THINK AS A GROUP WE'VE REALLY ADVOCATED THAT POSITION. I THINK WHAT WE'VE BEEN CONCERNED ABOUT IS THAT ENROLLMENT HAS BEEN VERY SLOW DESPITE THE FACT THAT THERE ARE OBVIOUSLY, YOU KNOW, TREMENDOUS NUMBERS OF THESE PROCEDURES BEING DONE. AND YOU KNOW, WE'RE JUST TRYING TO ADDRESS EVERY POTENTIAL BARRIER TO GET THE PATIENTS INTO THE STUDY.
THERE CLEARLY IS, I THINK IT SEEMS OBVIOUS TO ME, A LITTLE BIT OF A FINANCIAL DISINCENTIVE IF A PATIENT GETS ENROLLED, BECAUSE YOU ONLY HAVE A 50 PERCENT CHANCE OF ACTUALLY BEING ABLE TO DO THE PROCEDURE. IT'S IMPOSSIBLE FOR ME TO SAY HOW MUCH THAT DISINCENTIVE IS INFLUENCING ENROLLMENT, BUT IT JUST IS A CONCERN. AND YOU KNOW, WE HAVE BEEN STRUGGLING WITH THE FACT THAT IF THERE ARE REALLY 50,000 PROCEDURES BEING DONE IN THE UNITED STATES AND WE'RE ENROLLING A HUNDRED PATIENTS A YEAR IN CORAL, OR NOT MUCH MORE THAN THAT, THAT WE'RE GETTING .1 PERCENT OF ALL THE PROCEDURES, AND IT IS AN ISSUE FOR US.
BUT I THINK IT APPLIES NOT ONLY TO CORAL, IT APPLIES TO CLINICAL STUDIES IN GENERAL IN THIS

COUNTRY WHERE ENROLLMENT HAS TENDED TO BE LOW. BUT WE CERTAINLY HAVEN'T SUGGESTED AS A GROUP OR AS THE CORAL TRIAL, THAT FUNDING ONLY BE LIMITED TO PATIENTS ENROLLED IN THE CORAL STUDY.

DR. GARBER: WE WILL BE GETTING INTO A DISCUSSION OF THIS WHEN WE GET TO VOTING QUESTION NUMBER 4, AND HOPEFULLY THE SPEAKERS WILL STILL BE HERE TO ADDRESS QUESTIONS SPECIFICALLY ON THAT POINT. ANY OTHER QUESTIONS FOR THE PRESENTERS? STEVE?

DR. TEXTOR: I WONDER IF I COULD ASK DR. HIRSCH TO COMMENT A LITTLE BIT MORE ON THE GUIDELINES FROM THE AMERICAN HEART OR ACC, SPECIFICALLY AS TO THE ISSUE OF THE CLASS I RECOMMENDATION ABOUT PATIENTS WITH PULMONARY EDEMA, AND REALLY THE SERIES OF RECOMMENDATIONS BASICALLY ARGUING THAT IT'S REASONABLE TO UNDERTAKE REVASCULARIZATION FOR HYPERTENSION, PRESERVATION OF RENAL FUNCTION BASICALLY, GIVEN THE IIA RECOMMENDATION. THEY SEEM TO ME OPTIMISTIC COMPARED TO THE AHRQ RECOMMENDATIONS. HOW WOULD YOU RECONCILE THAT?

DR. HIRSCH: WELL, I WON'T TRY TO SPEAK DIRECTLY TO THE RECOMMENDATIONS THEMSELVES, BUT THE GUIDELINE WRITING COMMITTEE DID FEEL THAT THE CASE SERIES THAT EXISTED, THE LEVEL OF EVIDENCE A FOR

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THOSE INDICATIONS WERE NOT ADEQUATE TO ACHIEVE A CLASS I INDICATION, SO I CAN'T SPEAK MORE IN DETAIL TO THAT.

BUT I WOULD LIKE TO MAKE A COMMENT IF I COULD, THAT FOR THOSE CLASS I INDICATIONS AND THE IIA INDICATIONS, WE DO FEEL THERE IS COMPELLING EVIDENCE THAT MANY INDIVIDUALS IN OUR COUNTRY WOULD BENEFIT FROM MAINTAINING REIMBURSEMENT, THAT THERE IS AN ETHICAL STANDARD THAT CAN BE SUSTAINED THAT PERMITS THESE INTERVENTIONS TO IMPROVE HEALTH.

BUT YOU'RE RIGHT, THE EVIDENCE BASE IS INCOMPLETE AND I WOULD HAVE COMPLETED THAT WITH MY OTHER COMMENTS. WAS THERE AN ADDITIONAL QUESTION?

DR. TEXTOR: THE OTHER QUESTION, IT WAS ALLUDED THERE WAS SOME SORT OF MAJOR ETHICAL CONCERN, AND PERHAPS A REPRESENTATIVE FROM BOSTON SCIENTIFIC WOULD COMMENT ON THEIR ETHICAL RESERVATIONS ABOUT ENTERING PEOPLE IN THE CORAL TRIAL.

DR. GARBER: DR. KELLEY, CAN YOU COME UP TO THE MIKE, PLEASE?

DR. KELLEY: I THINK IT'S NOT ETHICAL IN THE SETTING OF THE TRIAL ITSELF, IT'S ETHICAL IN ASKING PATIENTS. IF YOU DECIDE UPON A COVERAGE THAT, YOU CAN ONLY HAVE A RENAL STENT IF YOU'RE PART OF A CLINICAL TRIAL, AND THE ONLY TRIAL IS A RANDOMIZED

00171

CLINICAL TRIAL, THAT PUTS PATIENTS IN A TOUGH POSITION, BECAUSE THEN THEY HAVE TO DECIDE WHETHER, A, YOU KNOW, IN THE INFORMED CONSENT THEY HAVE TO PARTICIPATE IN A CLINICAL TRIAL, AGAINST A TREATMENT THAT HAS BEEN OFFERED FOR THE LAST, YOU KNOW, TEN-PLUS YEARS.

DR. TEXTOR: REMIND ME WHAT THE ETHICAL BIND IS.

DR. GARBER: ARE YOU SAYING THAT IT IS KNOWN THAT THE TREATMENT IS EFFECTIVE, OR JUST BY VIRTUE OF HISTORY IT HAS BEEN AVAILABLE, AND THEREFORE IT'S POTENTIALLY UNETHICAL TO ONLY PROVIDE THE CONTEXT OF THE TRIAL. I THINK FROM MANY PEOPLE'S UNDERSTANDING OF ETHICS, IT'S ONE THING TO DENY A KNOWN EFFECTIVE THERAPY. IT'S QUITE ANOTHER TO DENY AN UNPROVEN THERAPY. AND I BELIEVE THAT THE RATIONALE FOR THE TRIAL IS THAT IT'S UNKNOWN WHETHER THIS IS EFFECTIVE.

DR. KELLEY: AND I AGREE ENTIRELY, AND I THINK THE COMMENTS THAT WERE MADE BY PEOPLE THAT IT'S NOT UNKNOWN IF IT'S THE RIGHT -- IT'S THE PATIENT SELECTION THAT POTENTIALLY IS NOT UNKNOWN, WHO ARE THE BEST PATIENTS TO BENEFIT FROM THIS THERAPY.

DR. GARBER: DR. HIRSCH, DID YOU WANT TO MAKE A COMMENT?

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DR. HIRSCH: THAT'S A VERY INTERESTING QUESTION, AND MANY PEOPLE IN THE AUDIENCE I THINK COULD SPEAK TO THAT. I THINK THAT WE MIGHT MAKE METAPHORS OF OTHER DISEASES WHERE WE HAVE AN INCOMPLETE EVIDENCE BASE, WHICH IS TRUE OF MANY CANCERS, FOR EXAMPLE, WHERE WE HAVE SOME EVIDENCE OF EFFICACY, IT'S INCOMPLETE, AND THE WRITING COMMITTEE ACKNOWLEDGED THAT. AND SOME PATIENTS REALLY DON'T HAVE ACCESS TO IT BASED ON REIMBURSEMENT FOR MEDICATIONS, ACCESS TO THEIR PHYSICIANS, TO PURE MEDICAL THERAPY ALONE.

SO I THINK THAT, ALAN, ONE CAN MAKE THE CASE THAT WHEN THERE IS A POTENTIAL THERAPEUTIC CHOICE BETWEEN TWO OR THREE DIFFERENT INDICATIONS, DIFFERENT TREATMENTS, AND IN A SENSE PATIENTS MAY ONLY HAVE ACCESS TO ONE OR THE OTHER PREFERENTIALLY, WE DO SET UP INHERENT BIASES BY REIMBURSING ONE VERSUS THE OTHER. SO PATIENTS END UP IN VERY UNIQUE CIRCUMSTANCES AND THE CLINICIAN WHO'S TREATING THE PATIENT DOES HAVE TO MAKE THAT BALANCE.

THERE'S SOME TREATMENT OFFERED. THESE ARE, AFTER ALL, DISEASES. ATHEROSCLEROTIC RENAL ARTERY STENOSIS HAS A VERY, VERY HIGH SHORT-TERM EVENT RATE. SO YOU LEAVE PATIENTS POTENTIALLY UNTREATED, IN A SENSE COERCED INTO NO TREATMENT IF

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YOU HAVE NO EQUIPOISE FOR REIMBURSEMENT. I HOPE THAT HELPS.

DR. GARBER: OKAY. THESE ARE INTERESTING POINTS. WE'RE GOING TO HAVE TO MOVE ON TO SOME MORE SPECIFIC QUESTIONS THAT ARE FACING US. YES?

DR. PRESSMAN: CONSIDERING WE'VE HEARD A FEW MINUTES AGO ABOUT THE SMALL NUMBER OF PEOPLE THAT ARE BEING RECRUITED TO STUDY, IT SEEMS TO ME WE SHOULD BE CONSIDERING APPROPRIATE CRITERIA FOR PERFORMING THESE PROCEDURES ON PATIENTS WHO ARE NOT RECRUITED FOR A STUDY, IF WE'RE GOING TO CONTINUE TO PAY FOR IT IN ANY FORMAT. AND I WOULD LIKE TO ASK DR. MURPHY, WHO REFERRED TO THAT EARLIER IN HIS COMMENTS, WHETHER OR NOT HE HAD ANY SUGGESTIONS OF SOME SORT OF INCLUSION CRITERIA FOR THE NON-CORAL STUDY PATIENTS.

DR. MURPHY: YEAH. THAT'S A GREAT QUESTION AND I THINK IS THE FUNDAMENTAL REASON FOR BEING HERE. THE GROWTH IN THE PROCEDURES IS SORT OF PARADOXICAL WHEN WE LOOK AT THE LITERATURE THAT CAME OUT DURING THE TIME PERIOD OF GROWTH, WHICH SUGGESTED THAT THE PROCEDURES DON'T PROVIDE A LOT OF BENEFIT. SO THE QUESTION IS, FOR THOSE OF US WHO DO THE PROCEDURES AND KNOW THAT WE'VE HAD PATIENTS WHO'VE GOTTEN BETTER, WHAT'S DISTINCT ABOUT THOSE INDIVIDUAL

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PATIENTS THAT WOULD ALLOW US TO CONTINUE TO OFFER SERVICES TO THOSE PATIENTS, ASSUMING THAT THERE'S GOING TO BE SOME COVERAGE FOR THE INTERVENTION IN GENERAL, WHICH I THINK THERE HAS TO BE. I DON'T THINK IT'S REASONABLE TO PULL THE RUG OUT FROM UNDER THE PROCEDURE IN TOTO AT THIS POINT IN TIME, BUT THERE HAS TO BE POTENTIALLY SOME GUIDELINES OR SOME REINING IN, SO THAT IT'S CLEAR AS TO WHO IS ELIGIBLE FOR THE PROCEDURE.

NUMBER ONE, I THINK THE PROPHYLACTIC STUFF IS POORLY JUSTIFIED. I THINK PEOPLE NEED SOME TYPE OF CLINICAL INDICATIONS. ALMOST ALWAYS THAT'S REFRACTORY BLOOD PRESSURE, CHRONIC KIDNEY DISEASE, AND IN SOME CASES HEART FAILURE, AND I'LL TALK MORE ABOUT THAT IN A MINUTE. BUT THE HYPERTENSION AS AN INDICATION SHOULD BE IN MY OPINION QUALIFIED BY HAVING PEOPLE UNDERGO FIRST DEDICATED MEDICAL MANAGEMENT ACCORDING TO THE JNC PROGRAM. AND IF THE BLOOD PRESSURE CAN'T BE CONTROLLED WITH THAT, AGAIN GETTING BACK TO THE PRINCIPLE OF FIRST DO NO HARM, TRY THE LESS INVASIVE MEANS FIRST AND EXHAUST THAT AVENUE. AND IF THAT DOESN'T WORK, THEN THE PERSON CAN BE CONSIDERED FOR INTERVENTION. SO THERE WOULD POTENTIALLY BE SOME PREQUALIFICATION BASED ON MEDICAL MANAGEMENT OF HYPERTENSION FAILING.

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AND ALSO, TO THROW IN WITH THAT, THERE HAS TO BE SOME THRESHOLD OF ANATOMY. A RENAL ARTERY STENOSIS OF 50 PERCENT WITH NO GRADIENT AND FAILED MEDICAL MANAGEMENT PROBABLY DOESN'T QUALIFY SOMEBODY. A STENOSIS OF, SAY, FOR EXAMPLE, 60 OR 70 PERCENT OR GREATER, PERHAPS WITH A PRESSURE GRADIENT AND REFRACTORY ON MEDICAL MANAGEMENT, WOULD BE A STRONG INDICATION FOR REIMBURSEMENT.

ON THE CHRONIC KIDNEY DISEASE SIDE, AN INDICATION OF CHRONIC KIDNEY DISEASE WOULD BE SUPPORTED IF THE PERSON HAD BILATERAL SEVERE STENOSES OR A SINGLE KIDNEY AND A SEVERE STENOSIS. ALSO, IT SHOULD BE A LONG-TERM OR AT LEAST SOME PERIOD OF TIME, IT SHOULDN'T BE A TRANSIENT KIDNEY FAILURE RELATED TO STATIN, ACE, OR DEHYDRATION OR SOME EPISODE OF SEPSIS OR WHATEVER THE CASE MAY BE.

AND THE LAST CLINICAL INDICATION WOULD BE THE HEART FAILURE INDICATION WHICH PATIENTS IN MY EXPERIENCE WOULD HAVE A STRONG CLINICAL BENEFIT FROM THE PROCEDURE, BUT ALMOST ALL OF THOSE HAVE BILATERAL DISEASE OR A SINGLE KIDNEY WITH SEVERE STENOSIS, AND THEY ALSO HAVE ELEMENTS OF CHRONIC KIDNEY DISEASE.

SO IF YOU'RE LOOKING FOR A LIST OF INDICATIONS FROM WHICH TO RUN THIS IN AS SORT OF A LITMUS TEST FOR A FIRST PASS AT A COVERAGE POLICY, I

THINK REFRACTORY HYPERTENSION AFTER DEDICATED MEDICAL MANAGEMENT WITH A SEVERE STENOSIS OR CHRONIC KIDNEY DISEASE WITH BILATERAL OR A SINGLE KIDNEY WITH SEVERE STENOSIS WOULD BE A GOOD PLACE TO START.

DR. GARBER: OKAY, THANK YOU. THIS IS ONLY NATURAL, IT HAPPENS ALL THE TIME, BUT WE'RE BORDERING INTO THE DISCUSSION OF THE VOTING QUESTIONS. SO, COULD I ASK THE SENSE OF THE PANEL, ARE WE READY TO GO?

DR. FENDRICK: ONE MORE.

DR. GARBER: GO AHEAD, MARK.

DR. FENDRICK: AND THIS BEING YOUR LAST PANEL, I THINK IT'S IMPORTANT FOR US TO THINK ABOUT THE INSTITUTIONAL HISTORY OF SEEING A NUMBER OF VERY PROMISING NONPHARMACEUTICAL INTERVENTIONS THAT HAVE A LOT OF INCREDIBLY TALENTED AND PASSIONATE INVESTIGATORS, AND WE'RE ALWAYS ASKING FOR MORE EVIDENCE. THE NAME OF THIS PANEL ACTUALLY CHANGED FROM THE MEDICARE COVERAGE ADVISORY COMMITTEE TO THE MEDICARE EVIDENCE DEVELOPMENT AND COVERAGE ADVISORY COMMITTEE, AND I THINK THAT WE WILL ALL BE ABLE TO TALK AT THE END OF THE DAY ABOUT THE LIMITATIONS OF RANDOMIZED TRIALS.

BUT I AM SOMEWHAT SURPRISED, GIVEN THAT EVERY ONE OF THE MAJOR PROFESSIONAL ORGANIZATIONS IS

HERE AND REPRESENTED, AND THE FACT THAT THERE IS NOW SEVERAL THOUSAND PROCEDURES A YEAR, THAT THERE HAS NOT BEEN CREATED AT LEAST A WELL-RUN REGISTRY THAT COULD AT LEAST GIVE US AN INFERENCE TO WHAT A RANDOMIZED TRIAL MIGHT SHOW. AND I JUST SAY THAT BECAUSE OF THE FACT THAN IN MOST OF THE OTHER MCACS I SAT ON, WE PUSHED FOR RCT, AND YOU PUSHED BACK SAYING THERE AREN'T ENOUGH SITES, IT TAKES TOO LONG, PATIENTS WON'T DO IT. BUT AT A MINIMUM, MANY OTHER INTERVENTIONAL FIELDS HAVE AT LEAST COME UP WITH, OF THE 30,000 FOLKS THAT HAVE BEEN STENTED OVER THE LAST FIVE YEARS -- I WOULD IMAGINE THERE ARE STILL A FEW PEOPLE IN AMERICA WITH RENAL ARTERY STENOSIS THAT HAVE NOT GOTTEN IT DONE, ALTHOUGH PROBABLY NOT IN MASSACHUSETTS OR TOLEDO, OHIO. BUT AT LEAST IN RHODE ISLAND, THERE'S PROBABLY A FEW FOLKS WITH RENAL ARTERY STENOSIS THAT HAVE NOT BEEN INTERVENED UPON. SO I WOULD REALLY -- I'M NOT PICKING ON ANY ONE INDIVIDUAL, BUT I'VE SEEN ENOUGH NODDING DURING MY COMMENTS THAT YOU DISCUSSED IT. AND SHORT OF RANDOMIZED TRIALS, AND MOST OF US DON'T WANT TO WAIT UNTIL 2010, THERE ARE ENOUGH SKILLED INVESTIGATORS AMONG YOU AND PEOPLE AT YOUR INSTITUTIONS WITH ABILITIES, METHODOLOGIC AND OTHER EXPERTISE, TO GIVE YOU REASONABLE ANSWERS TO AT LEAST

GET US A MAJOR STEP FORWARD FROM WHERE WE ARE NOW.
DR. GARBER: LET ME JUST ADD ONE POINT OF INFORMATION TO WHAT MARK SAID. OUR VOTING QUESTION 4 DOES NOT SAY THAT MEDICAL NATIONAL COVERAGE SHOULD BE LIMITED TO PATIENTS ENROLLED IN CLINICAL TRIALS. IT SAYS IN QUALIFIED CLINICAL RESEARCH STUDIES, SO IN FACT THIS DOES NOT MEAN THAT -- THEY ARE NOT ASKING US TO SAY EVERYONE WOULD NEED TO BE ENROLLED IN CORAL IN ORDER TO BE ELIGIBLE FOR REIMBURSEMENT. AGAIN, WE'LL GET TO THAT WHEN WE DISCUSS VOTING QUESTION 4.
DR. FENDRICK: THERE IS NO REGISTRY -- I SHOULD ASK THE QUESTION. AS FAR AS THE COUNTRY'S EXPERTS KNOW, THERE IS NO REGISTRY IN PLACE NOW.
DR. COOPER: AT THE DINGLE CENTER, YES.
DR. GARBER: THERE'S NO NATIONAL REGISTRY.
DR. HIRSCH: AND THERE'S NO REGISTRY THAT INCLUDES MEDICAL THERAPY EITHER.
DR. KRIST: I HAVE A CLARIFICATION QUESTION, NOT FOR ANYONE IN PARTICULAR. BUT WHEN WE SEE THE ONGOING STUDIES, THINKING ABOUT WHAT EVIDENCE DO WE HAVE, I SEE HERE FIVE OR SIX ONGOING STUDIES, BUT STAR, RAVE, ASTRAL AND NITER ARE ALL SUPPOSED TO BE DONE, AT LEAST LOOKING AT THE TIME LINES THAT I SEE. DO WE HAVE ANY INDICATION OF RESULTS OR WHEN WE MIGHT KNOW RESULTS, OR DOES ANYONE KNOW THIS?

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DR. COOPER: I HAVE BEEN IN CONTACT WITH THE HEAD OF THE STAR NETWORK AND ALSO THE ASTRAL NETWORK. I KNOW THAT STAR SOMETIME NEXT YEAR PROBABLY WILL PRESENT THEIR PRELIMINARY DATA. ASTRAL HAS FINISHED ENROLLMENT IN THEIR RANDOMIZED PHASE AND IS CONTINUING SOME OF THEIR CARDIAC REGISTRIES, AND I SUSPECT PROBABLY NEXT FALL WILL HAVE SOME RESULTS THERE.

RAVE IS A REGISTRY, I BELIEVE A SINGLE CENTER REGISTRY. I DON'T THINK THAT YOU'RE GOING TO GET EARTH-SHAKING NEWS FROM THAT.

DR. EDWARDS: DR. GARBER, COULD I SUBMIT ONE BRIEF COMMENT BEFORE WE -- I DON'T KNOW IF WE'RE READY TO PROCEED TO VOTING QUESTIONS, BUT IF IT'S OKAY, AS FAR AS THE VOTING QUESTIONS, BEFORE WE PROCEED TO THAT, I WANTED TO MAKE ONE POINT CLEAR THAT HAS BEEN ALLUDED TO BY MANY BUT NEVER OVERTLY STATED. AND THAT WOULD BE THE FACT THAT WE ARE VERY LIKELY DEALING WITH SPLIT CATEGORIES OF PATIENTS WHO MAY HAVE VERY DIFFERENT RESPONSES TO THERAPY, AND THE VOTING QUESTIONS DON'T BREAK THAT DOWN. I KNOW THAT WOULD CREATE A LIST OF ABOUT 25 QUESTIONS, I UNDERSTAND THAT.

BUT I THINK THAT A LOT OF DATA WHICH HAS BEEN ALLUDED TO BY SEVERAL OF THE PRESENTERS BUT

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EXCLUDED FROM THE WONDERFUL ANALYSIS BY THE TUFTS GROUP BECAUSE IT IS MOSTLY RETROSPECTIVE DATA, I THINK THERE IS STILL INFORMATION WITHIN ALL THOSE SCIENTIFIC STUDIES WHICH HAS SOME MERIT IN AT LEAST STATING THAT AND USING IT TO SORT OF SEPARATE THESE GROUPS, BECAUSE I THINK IT'S IMPORTANT TO THEORETICALLY UNDERSTAND THAT THERE ARE VERY DIFFERENT PATIENT POPULATIONS.

ONE IS THE FACT THAT EVEN IN ALL THE RETROSPECTIVE WORK THAT'S BEEN DONE OVER THOUSANDS OF PATIENTS, EVEN WITH VERY PRONOUNCED BLOOD PRESSURE DECREASES IN SOME OF THE SURGICAL GROUPS IN TERMS OF ABSOLUTE BLOOD PRESSURE DECREASE, BLOOD PRESSURE RESPONSE IN AND OF ITSELF HAS NEVER BEEN ASSOCIATED WITH A DECREASE IN ADVERSE EVENTS AND MORTALITY IN THE LIMITED NUMBER OF STUDIES THAT THAT'S BEEN LOOKED AT.

ALSO, AS MANY HAVE ALLUDED TO, SEVERE HYPERTENSION IS BECOMING A MORE INCREASINGLY RARE PHENOMENON BECAUSE OF THE INCREASE IN EFFICACY IN ANTIHYPERTENSIVE AGENTS. RENAL FUNCTION, ON THE OTHER HAND, HAS BEEN SHOWN BY SEVERAL INVESTIGATORS TO BE A FAIRLY ROBUST PREDICTOR AFTER INTERVENTION. IN OTHER WORDS, IF YOU HAD A GOOD RENAL FUNCTION RESPONSE, YOUR SUBSEQUENT FREEDOM FROM ADVERSE EVENTS

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AND SURVIVAL ARE BETTER. AND NOT ONLY THAT, BUT YOUR RESPONSE HAS SOMETHING TO DO WITH INITIAL FUNCTION. AND WHAT I MEAN THERE IS THERE'S SOME WORK THAT WAS DONE BY ONE OF MY MENTORS, I'VE NOT SEEN IT REPRODUCED BY ANYONE ELSE, BUT SAYING THAT IF YOU HAVE SEVERE RENAL INSUFFICIENCY, IF YOU IMPROVED TO ENJOY BETTER SURVIVAL THAN THOSE WHO WERE LEFT QUOTE-UNQUOTE STABILIZED, UNCHANGED OR WORSENED -- AS A MATTER OF FACT, THOSE LATTER TWO COHORTS, THEIR SURVIVAL ANALYSES WERE OVERLAPPING. HOWEVER, PATIENTS WITH LESSER DEGREES OF RENAL DYSFUNCTION OR NORMAL RENAL FUNCTION, THE ONLY GROUP THAT WAS SIGNIFICANTLY IMPACTED IN TERMS OF SURVIVAL WERE THOSE WORSENED.

AND I THINK THAT'S AN IMPORTANT POINT WHEN WE TALK ABOUT ANGIOPLASTY AND STENTING BECAUSE AS IT HAS BEEN ALLUDED TO, OVER THE SHORT HAUL, NOT NECESSARILY PERIPROCEDURALLY, BUT ANGIOPLASTY AND STENTING HAS BEEN ASSOCIATED WITH, PROBABLY CONSERVATIVELY, A 10 TO 20 PERCENT RATE OF HARMING RENAL FUNCTION, OR AT LEAST ASSOCIATED WITH DETERIORATING RENAL FUNCTION OVER SHORT-TERM FOLLOW-UP. AND IT IS UNKNOWN WHETHER THAT IS SECONDARY TO THE PROCEDURE, BUT A LOT OF PEOPLE, INCLUDING MYSELF, SUSPECT THAT IT IS.

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AND THAT APPLICATION OF PEOPLE WITH NORMAL RENAL FUNCTION AND HYPERTENSION, IF RENAL FUNCTION RESPONSE IS A BIG PREDICTOR OF OUTCOME, THAT'S BAD. WE MAY BE ACTUALLY HURTING PEOPLE WITH THE BEST OF INTENTIONS OF HELPING THEM.

NOW GIVEN ALL THAT INFORMATION, OUR GROUP IN PARTICULAR AND A LOT OF GROUPS, I THINK THE MAYO CLINIC GROUP AS WELL, HAVE REALLY STARTED TO SHIFT THEIR FOCUS TO PATIENTS WITH DECLINING RENAL FUNCTION AND SEVERE RENAL INSUFFICIENCY. AND THAT BRINGS ME BACK TO THE POINT THAT I THINK THERE ARE VERY DIFFERENT CATEGORIES. I THINK WITHIN HYPERTENSION THERE IS A REFRACTORY HYPERTENSION GROUP, BUT THEY PROBABLY NEED TO BE STUDIED SEPARATELY. THERE IS THE COMPLICATED HYPERTENSION GROUP, THOSE WITH FLASH PULMONARY EDEMA AND ALTERED CARDIAC DISTURBANCE SYNDROMES. AND THEN THERE'S THE PEOPLE WITH DECLINING RENAL FUNCTION.

I WOULD ALSO POINT OUT AS A LAST POINT THAT EVEN THOUGH DR. WEIBULL'S STUDY OF ANGIOPLASTY VERSUS SURGERY HAS BEEN QUOTED, WE ALL HAVE TO UNDERSTAND THAT THAT STUDY WAS DESIGNED, ITS ENDPOINTS WERE DESIGNED WITH AN INCREMENTAL INFERIOR RESULT OF ANGIOPLASTY AND STENTING BEING CONSIDERED EQUIVALENT TO SURGERY.

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NOW PLEASE DON'T GET ME WRONG. I'M NOT AT ALL CRYING FOR RETURN TO SURGERY, BUT WHAT I'M SAYING IS, I THINK IF YOU LOOK AT THE AGGREGATE LITERATURE, THE OUTCOMES IN TERMS OF RENAL FUNCTION RESPONSE WERE BETTER WITH SURGERY AND LESSER WITH ANGIOPLASTY AND STENTING, AND WE HAVE TO FIND OUT WHY THAT IS. BECAUSE FINDING THAT OUT WILL PROBABLY SHED A LOT MORE LIGHT ON, A, WHAT'S HAPPENING, AND B, WHAT ARE THE IMPORTANT PREDICTORS OF GOOD RESPONSES FOR FOLKS AFTER WE INTERVENE UPON THEM.

DR. GARBER: YOU MADE A NUMBER OF EXCELLENT POINTS. LET ME JUST SUGGEST A PROCEDURE SO THAT WE MAKE SURE THEY DON'T GET LOST IN OUR DISCUSSION AND VOTING PROCESS. QUESTIONS 1, 3 AND 4, VOTING QUESTIONS 1, 3 AND 4 ARE QUESTIONS, AND POSSIBLY ALSO 2, ARE QUESTIONS THAT COULD BE DIVIDED UP BY INDICATION. AND AS MATT SUGGESTED, I THINK THIS WAS NEVER CONSIDERED SERIOUSLY BECAUSE OF THE EFFECT IT WOULD HAVE ON THE LENGTH OF OUR DELIBERATION, SO IT'S NOT MEANT TO BURY ANY IMPORTANT FACTS.

SO WHAT I WANT TO SUGGEST AS A STARTING POINT FOR PROCEDURE IS IF YOU FEEL, FOR EXAMPLE, IN QUESTION 1 THAT IT IS IMPORTANT TO DISTINGUISH SOME PARTICULAR SUBGROUP OF PEOPLE, SAY FOR EXAMPLE IF YOU

THINK THAT THE EVIDENCE IS INADEQUATE GENERALLY BUT THERE'S A GROUP OF PEOPLE LIKE PEOPLE WITH DECLINING RENAL FUNCTION FOR WHICH THE EVIDENCE IS ADEQUATE, THEN YOU SHOULD STATE THAT AND AS A PANEL WE COULD DECIDE TO VOTE SEPARATELY ON THE QUESTIONS.

AN ALTERNATIVE, YOU WILL BE ASKED TO EXPLAIN THE WAY YOU VOTED AND YOU CAN STATE THAT YOU VOTED THIS WAY BECAUSE YOU WERE CONSIDERING SOME GROUP LIKE THAT.

INCIDENTALLY, ONE OF THE REASONS FOR NOT HAVING GONE THE ROUTE OF LISTING A BUNCH OF INDICATIONS IS THERE WAS NO CONSENSUS GOING INTO THIS, OR AT LEAST THAT WAS THE IMPRESSION OF STAFF, AND ALEX AND ME, THAT IF THERE'S NO CONSENSUS, IT'S GOING TO BE KIND OF HARD TO DECIDE WHICH CATEGORIES TO VOTE ON, AT LEAST BEFORE WE HAVE A DISCUSSION IN THE MEETING. BUT THAT SHOULD NOT PRECLUDE CREATING SOME CATEGORIES NOW IF ANYBODY FEELS STRONGLY ABOUT THAT.

SO I WOULD SUGGEST THAT WHEN WE GET TO QUESTION 1, AND ALSO QUESTIONS 3 AND 4 WHERE I THINK THIS IS RELEVANT, THAT WE HAVE A DISCUSSION, AND IF PEOPLE FEEL THAT THEY WANT TO DISTINGUISH SOME SUBGROUP, WE CAN VOTE SEPARATELY ON THAT.

I WANTED TO CHECK WITH MICHELLE WHETHER

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THAT'S FEASIBLE. OKAY. SO, DOES THAT ADDRESS YOUR CONCERNS IF WE GO THAT ROUTE?
DR. EDWARDS: ABSOLUTELY. I WASN'T TRYING TO CHANGE PROCEDURES, I JUST WANTED THE THOUGHT OUT THERE, BECAUSE I THINK IT IS IMPORTANT THAT WE THINK ABOUT THAT.
DR. GARBER: YEAH. BUT IF YOU DO THINK THERE IS A GROUP THAT'S REALLY DIFFERENT IN TERMS OF LEVEL OF EVIDENCE AND SO FORTH, THAT REALLY NEEDS TO COME OUT FROM OUR DELIBERATIONS TODAY.
DR. TEXTOR: COULD I ASK ONE EXTENSION OF THAT? IT STRIKES ME THAT PEOPLE ASKED ABOUT EARLY OUTCOMES FROM NITER AND THE STAR TRIAL. SEVERAL OF THOSE ARE BASED ON RENAL FUNCTIONAL END POINTS, AND I WANTED TO ASK DR. LINAS TO COMMENT. I THINK THERE ARE SOME MYTHS INVOLVED IN THE BASIS FOR SOME OF THESE TRIALS, MYTHS MEANING WIDELY VARYING ESTIMATES OF HOW MANY PEOPLE REACH END-STAGE RENAL DISEASE (INAUDIBLE). CAN YOU HELP CLARIFY, STU, HOW MANY PEOPLE WITH END-STAGE DISEASE ARE THERE BECAUSE OF RENOVASCULAR DISEASE, IN YOUR VIEW?
DR. LINAS: THANKS, STEVE, FOR ASKING THAT QUESTION. I THINK, CONSERVATIVELY SPEAKING, LOOKING AT THE USRDS DATA, THE NUMBER IS SOMEWHERE AROUND SIX OR SEVEN PERCENT. BUT OUR SENSE IS THAT THAT MAY BE

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HIGH AS WELL. IN THAT WHEN ONE LISTS A CAUSE OF END-STAGE RENAL DISEASE IN A PATIENT ENTERING A DIALYSIS PROGRAM, THERE ARE SOME DIAGNOSES THAT ARE PRETTY EASY. THAT IS, TYPE 2 DIABETES THAT HAS A PROTEINURIOPATHY, YOU CAN DO IT. SOMEONE WHO'S HAD AN EPISODE OF LUPUS NEPHRITIS, YOU CAN DO IT.
AND THEN THERE COMES DOWN A LIST OF I DON'T KNOW WHY THIS PATIENT HAS END-STAGE RENAL DISEASE, THEY DON'T HAVE A, B, C, D AND E. BY DEFAULT, THEY'VE BEEN HYPERTENSIVE. MAYBE THERE'S SOME RACE ISSUES HERE, AFRICAN-AMERICANS AREN'T SAID TO GET RENAL ARTERY STENOSIS, WHITE AMERICANS ARE. THEY DON'T HAVE PROTEINURIC RENAL DISEASE. THEY HAVE NOTHING THAT'S OBVIOUS, SO I'M GOING TO CHECK OFF THE BOX THAT SAYS RENAL ARTERY STENOSIS. SO THE DATA SAYS ABOUT SIX OR SEVEN PERCENT, BUT IN REALITY I THINK WE WOULD SAY IT'S PROBABLY HALF OF THAT IN REALITY.
BUT AFTER TELLING YOU THAT, KIND OF THE PROBLEM IS THE CORAL STUDY. EVEN IF THEY DON'T HAVE END-STAGE RENAL DISEASE, THEY ARE PRESUMABLY, IF THE DATA'S GOOD, AT RISK FOR CARDIOVASCULAR OUTCOMES, AND SO KNOWING WHETHER AN INTERVENTION IN THAT GROUP OF PATIENTS WOULD HAVE MADE A DIFFERENCE CARDIOVASCULARLY, WE DON'T KNOW.

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DR. SCHWARTZ: AND ALAN, THAT'S THE QUESTION I HAVE. I'M NOT SURE HOW TO PUT IT, BUT I THINK IN VOTING WE NEED TO BE CLEAR ABOUT WHY THIS PROCEDURE IS BEING DONE. IT SEEMS TO ME IT EVOLVES INTO ONE OF TWO CATEGORIES. ONE IS SALVAGE OR IMPROVEMENT OF RENAL FUNCTION, AND THE OTHER IS CARDIOVASCULAR EVENTS. I MEAN, THE REASON AS A GENERAL INTERNIST, I'M INTERESTED IN HYPERTENSION BECAUSE IT INCREASES CARDIOVASCULAR RISKS, EITHER MI OR STROKE OR THINGS LIKE THAT, AND THEY'RE VERY DIFFERENT. MOST OF THE EVENTS ARE GOING TO BE CARDIOVASCULAR EVENTS.

BUT THERE MAY BE SEPARATE INDICATIONS FOR RENAL FUNCTION, AND I THINK BY NOT SEPARATING THEM OUT, WE LEAD TO A MUDDINESS THAT FEELS A LITTLE UNCOMFORTABLE. SO I WONDER, AS WE GO THROUGH THESE, IF WE NEED TO JUST MAKE THOSE TWO DISTINCTIONS ON A BROAD BASIS THROUGHOUT.

DR. GARBER: I THINK WHAT, WE'LL DO THIS QUESTION BY QUESTION, AND IT WILL BECOME APPARENT WHETHER PEOPLE FEEL A NEED TO CARRY THROUGH ACROSS ALL THE QUESTIONS.

MY GUESS IS THAT THERE'S A DISTINCTION WE'RE NOT MAKING AT THIS POINT THAT'S GOING TO BECOME IMPORTANT LATER, WHICH IS, THERE'S A BELIEF ABOUT

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WHICH INDICATIONS ARE THE MOST PROMISING INDICATIONS. AND THERE'S ANOTHER ABOUT HOW MUCH EVIDENCE EXISTS. SO YOU MIGHT NOT FEEL THE SAME DISTINCTION IS NECESSARY FOR QUESTION 1 THAT YOU MIGHT THINK IS IMPORTANT, FOR EXAMPLE, FOR QUESTION 3. I DON'T WANT TO PRESUPPOSE HOW PEOPLE ARE GOING TO VOTE, BUT THE FIRST ONE IS PURELY A LEVEL OF EVIDENCE QUESTION.

DR. SCHWARTZ: THE OTHER THING I THINK WE NEED TO PUT IN QUESTION 1, MAYBE AS A 1.B, YOU COULD STILL HAVE A CERTAIN LEVEL OF CONFIDENCE FOR THE THREE CATEGORIES OR THREE PROCEDURAL AREAS THAT ARE ASKED FOR, BUT THEY COULD BE DIFFERENT. FOR EXAMPLE, YOU MIGHT HAVE A CERTAIN LEVEL OF CERTAINTY FOR THE SAFETY AND EFFICACY OF THE ANGIOPLASTY, BUT YOU MIGHT FEEL COMFORTABLE ABOUT WITH STENT THAN WITHOUT STENT, AND I'M NOT SURE THAT'S CAPTURED BY HOW YOU'RE ASKING THE QUESTIONS.

DR. GARBER: WHY DON'T WE START OUR DISCUSSION AND SEE HOW THAT SHAKES OUT. THIS IS ALL LEADING UP TO, SINCE WE'RE ANTICIPATING WHAT WE'RE GOING TO SAY IN DISCUSSION, SO WHY DON'T WE GET RIGHT TO IT? HAS EVERYBODY HAD A CHANCE TO READ QUESTION 1? I THINK CMS PUT THIS QUESTION IN FOR A REASON, SO I THINK THE ANSWER WOULD BE NO DATA IF THAT'S WHAT

YOU BELIEVE.
DR. COOPER: THERE ARE NONE UNDER INVESTIGATION.
DR. GARBER: SO NO DATA NOW AND THERE WON'T BE DATA, THAT'S WHAT WE'RE HEARING.
DR. PRESSMAN: IS IT INAPPROPRIATE TO ADD MEDICAL THERAPY AS ONE OF THE QUESTIONS IN NUMBER 1?
DR. GARBER: WELL, THESE, I BELIEVE, ARE ALL COMPARED TO MEDICAL THERAPY. NOW YOU COULD ADD A QUESTION ABOUT MEDICAL THERAPY BETTER THAN PLACEBO, BUT I THINK THE PRESUMPTION HERE WAS THAT AS A BASELINE, PEOPLE WOULD BE RECEIVING MEDICAL THERAPY FOR HYPERTENSION.
DR. PRESSMAN: BUT THE PRESUMPTION SUGGESTS IT'S THE GOLD STANDARD, AND I DON'T THINK WE HAVE THAT INFORMATION.
DR. GARBER: NO, IT JUST PRESUMES IT'S THE STANDARD.
DR. PRESSMAN: BUT THAT'S MY CONCERN. I DON'T THINK -- I MEAN, WHAT WE'VE HEARD TODAY AND WHAT WE'VE READ, WE HAVE NO DATA TO INDICATE THAT.
DR. SCHWARTZ: IN THEORY, YOU KNOW, I WAS THINKING A LOT ABOUT THAT SINCE I READ ALL THIS MATERIAL IN PREPARATION. IF WE WEREN'T TALKING ABOUT THIS SPECIFIC CONDITION, I'D HAVE THE SAME PROBLEM.

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THE ASSUMPTION IS THAT IF THERE ARE NO DATA THAT THE MEDICAL PROCEDURE MUST BE THE STANDARD THAT WE'RE COMPARING IT TO. I THINK IN THIS PARTICULAR CASE, THOUGH, THERE IS A GOOD REASON FOR BELIEVING THAT, AND THAT IS AS WAS STATED BY SEVERAL OF THE SPEAKERS, ALL THESE PEOPLE HAVE INDICATIONS FOR AGGRESSIVE CARDIOVASCULAR RISK PREVENTION ANYWAY, BECAUSE THEY HAVE VASCULAR ATHEROSCLEROSIS. THEY SHOULD ALL BE ON STATINS, AND OUTSIDE OF THE RENAL ARTERIES, THEY SHOULD ALL BE TREATED FOR THEIR HYPERTENSION. SO IN THIS PARTICULAR CASE, I THINK THERE IS, I FEEL COMFORTABLE SAYING WHAT DOES THIS ADD TO SOMETHING EVERYBODY SHOULD BE GETTING. ALTHOUGH I AGREE, WE DON'T KNOW IF THAT IS DOING ANYTHING MORE FOR THE RENAL ARTERY STENOSIS.

DR. GARBER: LINDA.

DR. BERGTHOLD: I DON'T LIKE ANSWERING QUESTIONS WHERE THERE ARE TWO SORT OF ENDPOINTS. YOU'RE TALKING ABOUT TWO THINGS. YOU'RE ASKING US TO EVALUATE SAFETY AND CLINICAL EFFECTIVENESS. CAN WE SEPARATE THEM OUT OR DO YOU THINK IT DOESN'T MATTER?

DR. CHARYTAN: I AGREE WITH THAT BECAUSE THERE MIGHT BE GOOD DATA ON THE SAFETY OF THE PROCEDURE, WHICH IS QUITE SEPARATE FROM WHETHER THE PROCEDURE IS EFFECTIVE.

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DR. GARBER: WELL, STEVE IS NOT HERE, SO LET ME TAKE A STAB AT TRYING TO ANSWER ON HIS BEHALF, AND THEN MARCEL CAN CORRECT ME. BUT SOME OF THE COMPLICATIONS OF THE PROCEDURE ARE ACTUALLY THE THINGS THE PROCEDURE IS DESIGNED TO PREVENT, AND GETTING TO AN ARGUMENT ABOUT WHETHER THAT'S A RISK OF THE PROCEDURE OR FAILURE TO PREVENT IT OR SOMETHING IS NOT VERY HELPFUL. SO I THINK THE CONCEPT HERE IS, DOES IT PROVIDE A NET HEALTH BENEFIT? IRRESPECTIVE OF WHETHER YOU CALL SOMETHING A SAFETY ISSUE OR NOT, I MEAN, YOU CAN TALK ABOUT RELATIVELY NARROW DEFINITIONS OF SAFETY ISSUES, BUT YOU THINK ABOUT COMPLICATIONS AND THINGS LIKE EMBOLI, AND SOME OF THOSE MAY ALSO BE REFLECTIONS OF THE UNDERLYING DISEASE PROCESS. SO THE IDEA HERE IS REALLY ABOUT NET HEALTH BENEFIT AND NOT AN ATTEMPT TO DISTINGUISH, I DON'T THINK THEY CARE A LOT ABOUT DISTINGUISHING WHAT THE SPECIFIC SAFETY CONCERNS ARE FROM THE PROCEDURE. BARRY?

DR. PRESSMAN: SOMEONE WANTS TO SAY SOMETHING.

DR. GARBER: YES, DR. SOS?

DR. SOS: WELL, CAN I COMMENT ON --

DR. SALIVE: WAIT. LET ME JUST ADDRESS THIS. I THINK IF I UNDERSTOOD THE QUESTION, YOU'RE

CONCERNED ABOUT NUMBER 1 BUT ALSO NUMBER 3, OR JUST NUMBER 1, BECAUSE I THINK ALAN ADDRESSED NUMBER 3 PRETTY WELL. SO YOU KNOW, NUMBER 3 IS SORT OF A COMBINATION OF THE TWO INTO NET HEALTH BENEFITS, I THINK IMPROVED KEY HEALTH OUTCOMES IS HOW WE PHRASED IT IN THIS VERSION.

BUT IF YOU FOCUS ON NUMBER 1, IT'S ADEQUACY OF THE EVIDENCE, OKAY? I MEAN ANY EVIDENCE, ALL THE EVIDENCE, THE TOTALITY OF EVIDENCE IS WHAT WE'RE ASKING ABOUT. AND CERTAINLY, YOU KNOW, WITHIN A TOTALITY OF EVIDENCE, IT HAS DIFFERENT AMOUNTS FOR A RARE SAFETY ENDPOINT VIS-A-VIS, YOU KNOW, A DIFFERENT LEVEL OF ADEQUACY PERHAPS FOR THE MAIN EFFECTIVENESS OUTCOMES. WE'LL GRANT YOU THAT, BUT WE'RE REALLY ASKING ABOUT THE ADEQUACY OF THE BODY OF EVIDENCE TO ASSESS THESE SETS OF TREATMENTS.

DR. GARBER: DR. SOS.

DR. SOS: I'VE HEARD A LOT OF DISCUSSION ON THE PANEL NOW ABOUT INDICATIONS, AND ONE WAS THE RECURRENT FLASH PULMONARY EDEMA WITH BILATERAL DISEASE AND WAS IT ASSOCIATED WITH RENAL DYSFUNCTION. THE SECOND WAS RAPIDLY PROGRESSING RECENT ONSET DYSFUNCTION, AND THE THIRD WAS HYPERTENSION. UNFORTUNATELY, THERE IS A VERY IMPORTANT FOURTH ONE, WHICH MAY ACCOUNT FOR THE VAST MAJORITY OF THE 30,

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40,000, HOWEVER MANY, AND THAT IS PATIENTS WHO MAY HAVE HYPERTENSION AND MAY HAVE RENAL ARTERY DISEASE, BUT THEY ARE NOT IN ANY WAY RELATED.
AND I THINK THAT THAT NEEDS TO BE CONSIDERED VERY SIGNIFICANTLY BY YOU, BECAUSE I WILL BET ANYTHING THAT THE VAST INCREASE IN THE NUMBER OF PATIENTS BEING TREATED IS NOT FOR -- YOU CAN AGREE OR DISAGREE WHETHER HYPERTENSION OR RENAL DYSFUNCTION IS AN INDICATION IF IT IS RELATED TO THE STENOSIS. I'M MUCH MORE CONCERNED ABOUT THE COINCIDENCE OF RENAL ARTERY STENOSIS WHICH MAY BE A 20 OR 30 PERCENT STENOSIS WHICH IS BEING TREATED IN SOMEBODY WHO MAY OR MAY NOT BE HYPERTENSIVE, AND WHERE THERE'S NOT EVEN AN ATTEMPT TO GET A GRADIENT ACROSS THIS. AND I THINK THAT THAT OUGHT TO BE A VERY IMPORTANT PART OF YOUR DISCUSSIONS.
DR. GARBER: OKAY, THANK YOU. SO WE'RE ON VOTING QUESTION 1, YOU'VE HAD A CHANCE TO REVIEW THE QUESTION, WE'VE HAD PRE-DISCUSSION, AND NOW WE CAN HAVE DISCUSSION.
DR. SCHWARTZ: THE ONLY THING I WOULD SAY BEFORE WE GET INTO IT, I WOULD FEEL MORE COMFORTABLE IF WE SEPARATED SAFETY AND CLINICAL EFFECTIVENESS, BECAUSE I THINK THERE ARE SOME SITUATIONS WHERE I FEEL COMFORTABLE ABOUT THE DEGREE OF SAFETY

INFORMATION A LOT MORE THAN I DO ABOUT ITS MEDICAL EFFECTIVENESS. SO, I WONDER IF WE COULD JUST DRAW A COLUMN DOWN AND VOTE ON THESE THINGS TWICE.

DR. GARBER: OKAY.

DR. MAISEL: I MAY BE STANDING ALONE ON THE PANEL, BUT I THINK THEY NEED TO BE CONSIDERED TOGETHER. I THINK THAT THERE ARE MEASURES OF EFFECTIVENESS THAT ARE ALSO OR POTENTIALLY COULD BE VIEWED AS SAFETY. I THINK IT'S HARD TO JUDGE SAFETY WITHOUT KNOWING THE CLINICAL BENEFIT OR THE EFFECTIVENESS, SO I THINK THE TWO ARE INEXTRICABLY ENTWINED.

DR. GARBER: FIRST OF ALL, LET ME JUST TAKE A STRAW POLL. HOW MANY PEOPLE WOULD PREFER TO VOTE SEPARATELY ON SAFETY AND EFFECTIVENESS?

(SHOW OF HANDS.)

HOW MANY WOULD PREFER TO LINK THEM?

(SHOW OF HANDS.)

ESPECIALLY IF YOU COUNT VOTING MEMBERS, THERE'S A CLEAR CONSENSUS.

SO LET ME JUST REPEAT, THIS WAS ONLY EVIDENCE ADEQUACY, NOT -- BILL, DID YOU WANT TO MAKE A STATEMENT?

DR. MAISEL: I JUST HAD ANOTHER INTERESTING QUESTION FOR THE PANEL I'M STRUGGLING

WITH A LITTLE BIT, WHICH IS THE ISSUE OF SURROGATE ENDPOINTS AND WHAT EXACTLY WE WANT TO JUDGE THIS QUESTION ON. CERTAINLY WE ALL RECOGNIZE HYPERTENSION IS A PROBLEM, THAT LOWER IS GENERALLY BETTER WITH REGARD TO THE GUIDELINES, BUT WE ALSO NEED TO ACKNOWLEDGE THAT THERE ARE SOME MEDICATIONS THAT LOWER BLOOD PRESSURE THAT HAVE A DIFFERENT MORTALITY BENEFIT THAN ANOTHER MEDICATION, AND I'M NOT SO SURE I'VE SEEN ANY DATA THAT A REDUCTION IN CREATININE OR AN IMPROVEMENT IN GFR ACTUALLY TRANSLATES INTO A CLINICAL BENEFIT FOR THE PATIENT. OBVIOUSLY THE CORAL STUDY WILL HELP A LOT WITH CARDIOVASCULAR OUTCOMES, BUT THESE ARE SICK PATIENTS WHO ARE GOING TO HAVE CARDIOVASCULAR EVENTS AND WHETHER THEIR CREATININE IS 1.8 OR 1.4, I'M STRUGGLING TO SEE IF THAT'S REALLY A CLINICAL BENEFIT FOR THE PATIENT.

DR. GARBER: I'M GOING TO TAKE A CHANCE SPEAKING FOR STEVE AND MARCEL HERE, BUT I THINK THE QUESTION REFERS TO FINAL HEALTH OUTCOMES, NOT JUST SURROGATE ENDPOINTS. IF YOU BELIEVE THERE IS GOOD DATA SUPPORTING THAT THE INTERVENTION IN QUESTION IMPROVES SURROGATE ENDPOINTS AND, FURTHERMORE, IF YOU ARE ENTIRELY CONFIDENT THAT AN IMPROVEMENT IN SURROGATE ENDPOINT TRANSLATES INTO AN IMPROVEMENT IN FINAL ENDPOINT, THEN YOU WOULD VOTE THAT THERE IS

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ENOUGH EVIDENCE. IF YOU HAVE QUESTIONS ABOUT THAT CONNECTION BETWEEN SURROGATE ENDPOINTS AND FINAL ENDPOINTS AND YOU THINK THERE IS ONLY EVIDENCE ON SURROGATE ENDPOINTS, THEN YOU WOULD PRESUMABLY NOT BE CONFIDENT AT ALL IN YOUR RESPONSE TO THE QUESTIONS. MARK?

DR. FENDRICK: THIS IS A QUESTION I ASK EVERY TIME, AND I KNOW YOU ANSWER IT BEAUTIFULLY, BUT THE DIFFERENCE BETWEEN UNCERTAIN AND NOT CONFIDENT IN THE CONTEXT OF THIS QUESTION?

DR. SALIVE: UNCERTAIN IS NOT QUITE BELIEVED.

DR. FENDRICK: THANK YOU, MARCEL.

DR. SCHWARTZ: SO THEN YOU WOULD BE DEALING WITH BETWEEN A THREE OR A ONE.

DR. FENDRICK: NO, BECAUSE IN PREVIOUS QUESTION, A THREE MEANT INJURIOUS -- I'M SORRY, ONE MEANT INJURIOUS. I WILL, IF YOU DON'T MIND, TAKE THE LIBERTY TO TALK ABOUT DRUG-ELUTING STENTS AND SINCE THERE ARE NO DATA, I THINK UNCERTAIN IS A VERY FAIR ANSWER. BUT WHEN THERE ARE DATA BUT YOU'RE NOT SURE, IS THAT THREE OR ONE?

DR. GARBER: SO IF YOU ARE CONFIDENT ABOUT THE DATA, YOU WOULD RANK THAT AS SOME HIGH NUMBER FOR NUMBER 1. AND IF YOU'RE CONFIDENT THAT IT SHOWS

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HARM, THEN YOU WOULD GIVE IT A ONE ON QUESTION 3.
(INAUDIBLE COLLOQUY BETWEEN PANELISTS.)
DR. GARBER: LET ME JUST MAKE A QUICK SUGGESTION. YOU'RE MAKING A PERFECTLY APPROPRIATE AND PERFECTLY LOGICAL POINT. I THINK WE CAN HANDLE THAT PART IN DISCUSSION RATHER THAN REVISING THE DEFINITIONS. BUT LET'S DO THE VOTE AND THEN YOU CAN EXPLAIN, IF YOU FEEL THAT WAY, THAT YOU'RE CONFIDENT THAT IT'S NOT GOOD FOR YOU, OR HOWEVER YOU WANT TO PUT IT, MARK. IT'S A VERY VALID POINT, THAT THERE IS A WEAKNESS IN THIS SCORING SYSTEM.
DR. FENDRICK: YOU ANSWERED IT PERFECTLY. THANK YOU.
DR. GARBER: SO, DOES EVERYBODY -- I JUST REALIZED, IT'S POSSIBLE THAT NOT EVERYBODY WHO'S VOTING HERE HAS GONE THROUGH THIS VOTING PROCEDURE BEFORE, BUT WHEN YOU DECIDE WHAT SCORE YOU WANT TO GIVE IT, ONE BEING NOT CONFIDENT AT ALL, FIVE BEING HIGHLY CONFIDENT, JUST PUT OUT YOUR FLASH CARD WHEN I CALL FOR THE VOTE, AND THEN SOMEBODY IS GOING TO RECORD ALL THE SCORES, SO YOU NEED TO HOLD IT UP LONG ENOUGH FOR THAT.
MS. ATKINSON: ALSO, YOU RECEIVED BALLOTS, AND YOU WILL WRITE YOUR SCORE ON YOUR BALLOTS FOR EACH QUESTION, AND THEN MARIA WILL COME AROUND AND

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PICK UP THE BALLOTS. SO YOU'RE DOING THE CARDS SO IT SHOWS FOR THE PUBLIC AND FOR THE RECORD, AND THEN WE USE THE BALLOTS TO PUT IT INTO THE SPREADSHEET.
DR. BERGTHOLD: SO IN OTHER WORDS, THEY SHOULD BE THE SAME.
MS. ATKINSON: YES, PLEASE.
DR. GARBER: OKAY. ARE PEOPLE READY TO VOTE ON 1.A?
DR. PRESSMAN: COULD I ASK ONE FURTHER QUESTION? IF I'M CONFIDENT THAT THE DATA SHOWS SOMETHING IS UNSAFE, IS THAT A FIVE OR A ONE?
DR. GARBER: THAT'S A FIVE, BUT THAT'S IF YOU'RE HIGHLY CONFIDENT THAT THE DATA ARE ADEQUATE. ONE OF THE REASONS FOR THIS QUESTION THAT'S DISTINCT FROM GOOD OR BAD IS ARE FURTHER STUDIES LIKELY TO BE NEEDED. SO IF YOU'RE HIGHLY CONFIDENT THAT IT IS HARMFUL, FOR EXAMPLE, FOR THIS ONE YOU SHOULD ANSWER FIVE. AGAIN, IN THE DISCUSSION, WE WANT YOU TO MAKE THAT STATEMENT SO THAT IT'S NOT INTERPRETED THE OPPOSITE OF WHAT IT MEANS.
DR. CHARYTAN: YEAH. THE QUESTIONS, SO THE PEOPLE READING OR LOOKING AT THE FINAL VOTE UNDERSTAND WHAT THE VOTE MEANT.
DR. GARBER: RIGHT, AND THAT REALLY SHOULD GO INTO NUMBER 3, BUT OUR SCORING SYSTEM DOESN'T

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REALLY --
DR. SCHWARTZ: SO THE REASON FOR ONE ISN'T
HOW BAD (INAUDIBLE).
DR. GARBER: WELL, YEAH, THE REASON FOR
THAT IS THE PRINCIPAL ONE, DEFINITELY, THAT IS, IF
THE EVIDENCE IS ADEQUATE TO DRAW CONCLUSION, THEN IF
IT IS, WE DON'T NEED TO TALK ABOUT THIS INDICATION,
MEDICARE NEEDS TO FIGURE OUT A WAY TO DEVELOP MORE
EVIDENCE. IS THAT FAIR? OKAY.
LET ME ASK YOU TO VOTE THEN, 1.A, SURGICAL
RENAL ARTERY RECONSTRUCTION, HOW CONFIDENT ARE YOU
THAT THE EVIDENCE IS ADEQUATE?
(MEMBERS OF THE PANEL VOTED, RESULTS WHICH
WERE RECORDED BY STAFF.)
DR. GARBER: OKAY.
NOW I GUESS WE COULD ASK AT THIS POINT OR
IN NUMBER 3, BUT HOW MANY PEOPLE WHO ARE CONFIDENT
WERE CONFIDENT THAT IT DOESN'T WORK?
(SHOW OF HANDS.)
MR. LACEY: IT SEEMS TO HAVE A ROLE FOR A
VERY SMALL SUBSET OF PATIENTS, BUT A VERY HIGH RISK
OF COMPLICATIONS AND SIGNIFICANT MORBIDITY, SO FROM
THE DATA THAT I'VE SEEN --
DR. GARBER: FOR BOTH PEOPLE IT HARMS AND
PEOPLE IT HELPS.

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MR. LACEY: YEAH. SANDY?
DR. SCHWARTZ: I INTERPRET IT THE SAME WAY. I DON'T SEE ANYBODY OUT THERE WHO WANTS TO DO STUDIES OF SURGERY, YOU KNOW.
DR. GARBER: OKAY. LET'S DO B, THIS IS ANGIOPLASTY WITHOUT STENT REPLACEMENT. AGAIN, WE'RE VOTING ON CONFIDENCE IN THE AMOUNT OF EVIDENCE.
(MEMBERS OF THE PANEL VOTED, RESULTS WHICH WERE RECORDED BY STAFF.)
DR. GARBER: DOES ANYBODY WANT TO EXPLAIN THEIR VOTES, ESPECIALLY PEOPLE THAT GAVE IT FIVE, IN THE SENSE THAT IT'S BENEFICIAL OR QUESTIONS ABOUT THAT?
DR. EDWARDS: I'M A NONVOTING MEMBER, BUT I WOULD SAY THAT I THINK THAT THE DATA FOR ANGIOPLASTY ALONE IS STRONG AND THAT IT WOULD NOT BE BENEFICIAL, AT LEAST FOR ATHEROSCLEROTIC DISEASE.
DR. GARBER: ANY OTHER COMMENTS?
DR. SLAUGHTER: I WOULD AGREE THAT THERE IS A LACK OF EVIDENCE FOR CLINICAL EVIDENCE, BUT I DON'T THINK THERE'S ENOUGH EVIDENCE TO TRULY SORT OF DRAW A CONCLUSION. IT'S VERY LIMITED FOR SHORT-TERM FOLLOW-UP, AND ANYTHING SIX MONTHS OR LESS REALLY GIVES YOU NO IMPRESSION OF LONG-TERM REDUCTION IN CARDIOVASCULAR RISKS AND WHETHER OR NOT THEY WOULD BE

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IMPACTED.
DR. GARBER: OKAY, THANK YOU.
DR. SCHWARTZ: AND I HAVE QUESTIONS ABOUT, I'M NOT CONFIDENT, BECAUSE I'M PRETTY CONFIDENT IT'S NOT AS EFFECTIVE AS DOING IT WITH STENTS, BUT CLINICALLY I THINK IT IS IMPORTANT.
DR. GARBER: IS THAT A GENERAL CONSENSUS, WHAT MARK AND SANDY JUST SAID? LET THE RECORD REFLECT YES.
OKAY. NOW WITH BARE METAL STENTS, 1.C.
(MEMBERS OF THE PANEL VOTED, RESULTS WHICH WERE RECORDED BY STAFF.)
DR. GARBER: OKAY. THANK YOU. DOES ANYBODY WANT TO EXPLAIN THEIR VOTES ON THIS ONE? I THINK THEY WERE MOSTLY SELF-EXPLANATORY, BUT I COULDN'T SEE IF ANYONE GAVE IT A FOUR OR FIVE.
OKAY. NOW, WE JUST HAD A DISCUSSION ABOUT THE DRUG-ELUTING STENTS, SO THE QUESTION IS -- THIS PARTICULAR ONE, FIRST WE'RE GOING TO VOTE ON CONFIDENCE AND THE LEVEL OF EVIDENCE FOR DRUG-ELUTING.
(MEMBERS OF THE PANEL VOTED, RESULTS WHICH WERE RECORDED BY STAFF.)
DR. GARBER: WE MAY GET A UNANIMOUS VOTE HERE.

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DR. CHARYTAN: THE PROBLEM WITH DRUG-ELUTING STENTS, DOESN'T THAT DEPEND ON FIRST DEMONSTRATING THAT STENTING HAS A BENEFIT AND THAT DRUG-ELUTING STENT HAS AN ADDED, PRESUMED ADDED BENEFIT OF MAINTAINING PATENCY? WHEREAS HERE, WE'RE ARGUING WHETHER THERE'S ANY BENEFIT OF THE PROCEDURE AT ALL, SO WORRYING ABOUT WHETHER THE DRUG-ELUTED STENT ADDS TO THAT OR NOT IS REALLY A QUESTION THAT FOLLOWS. THAT NEEDS AN ANSWER TO THE FIRST QUESTION, DOES INTERVENTION GIVE ANY BENEFIT, AND THEN YOU CAN WORRY ABOUT FINDING THE EXACT TECHNOLOGY TO MAXIMIZE THAT BENEFIT.

DR. GARBER: I THINK THAT'S A VERY GOOD RATIONALE FOR HOW THE VOTE ACTUALLY WENT, BECAUSE I THINK EVERYBODY GAVE THAT A ONE. SO, DOES ANYBODY DISAGREE, OR DOES EVERYONE PRETTY MUCH AGREE WITH WHAT CHAIM SAID? OKAY.

DR. FENDRICK: AND CHAIM'S POINT GETS TO QUESTION 3.

DR. GARBER: YES. OKAY. NOW, FIRST OF ALL, CONGRATULATIONS. DOES EVERYBODY HAVE A GOOD EXPLANATION AS WELL FOR VOTING THE WAY THEY DID? I DON'T CARE HOW YOU VOTED, I JUST CARE THAT IT ACCURATELY REFLECTED YOUR BELIEFS, AND SO FAR WE'RE DOING PRETTY WELL.

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NUMBER 2, BASED ON THE EVIDENCE PRESENTED, HOW CONFIDENT ARE YOU THAT PUBLISHED RESULTS APPLY TO THREE DIFFERENT GROUPS? THE FIRST IS THE PATIENT POPULATION, DOES IT APPLY TO MEDICARE PATIENTS WITH TYPICAL COMORBIDITIES, PRESUMABLY MEANING TYPICAL MEDICARE BENEFICIARIES WHO WOULD AT LEAST BE A CANDIDATE FOR THE PROCEDURE.

DR. SCHWARTZ: HOW IS THAT DIFFERENT FROM B?

DR. GARBER: QUESTION 1 IS INTENDED TO ADDRESS JUST IN GENERAL IN ANY POPULATION, BUT QUESTION 2 IS SPECIFICALLY, I'M NOT SAYING THAT'S THE CASE HERE, BUT OFTENTIMES WE LOOK AT TECHNOLOGY AND --

(INAUDIBLE COLLOQUY AMONG PANELISTS.)

DR. GARBER: OKAY. 2.B AND 2.C, I'M GOING TO READ THE VOTING QUESTIONS, OKAY, AND THAT WHAT YOU SHOULD VOTE ON, NOT WHAT'S TYPED ON THE BALLOT. SO 2.A SAYS, HOW CONFIDENT ARE YOU THAT THE PUBLISHED RESULTS APPLY TO MEDICARE PATIENTS WITH DIFFICULT COMORBIDITIES?

(MEMBERS OF THE PANEL VOTED, RESULTS WHICH WERE RECORDED BY STAFF.)

DR. GARBER: SO DO THESE RESULTS APPLY EITHER DIRECTLY OR GENERALIZED TO THE MEDICARE

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POPULATION. OKAY. DOES ANYBODY WANT TO MAKE ANY COMMENTS ABOUT WHY THEY VOTED AS THEY DID, OR IS IT SELF-EVIDENT? OKAY.

2.B. NOW THIS IS ABOUT PROVIDERS. IT SAYS, HOW CONFIDENT ARE YOU THAT THE PUBLISHED RESULTS APPLY TO PROVIDERS, I.E., FACILITIES OR PHYSICIANS IN COMMUNITY PRACTICE? IN OTHER WORDS, WERE THE TRIALS CONDUCTED BY A TOTALLY DIFFERENT TYPE OF PROVIDERS, OR THE PUBLISHED STUDIES DONE BY DIFFERENT PROVIDERS.

(MEMBERS OF THE PANEL VOTED, RESULTS WHICH WERE RECORDED BY STAFF.)

DR. GARBER: OKAY. LINDA, DID YOU WANT TO SAY SOMETHING?

DR. BERGTHOLD: YEAH. I JUST WANT TO MAKE A COMMENT ABOUT WHY I VOTED ONE, AND AS SORT OF THE PROTECTOR OF THE PATIENTS' RIGHTS, I WAS SURPRISED TO HEAR THE TESTIMONY TODAY AND HOW COMPLICATED THESE PROCEDURES ARE, AND TO THINK THAT THESE PROCEDURES COULD BE DONE IN COMMUNITY HOSPITALS BY DOCTORS WHO ARE NOT WELL TRAINED CONCERNED ME. SO I'M NOT CONFIDENT THAT THE STUDY RESULTS SHOW THAT IF THIS KIND OF PROCEDURE IS BEING DONE, IT SHOULD BE DONE AT CENTERS OF EXCELLENCE, IT SHOULD BE DONE IN LOCALES WHETHER THE PHYSICIANS ARE VERY WELL TRAINED AND

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SUPERVISED.
DR. CHARYTAN: I'D LIKE TO COMMENT ON THAT COMMENT, IF I MAY. ALTHOUGH THE LAST INTERVENTION WAS DONE AS EARLY AS IN THE '40S, I THINK THIS ISSUE IS LESS, ALTHOUGH A QUESTION OF WELL TRAINED INTERVENTIONS SO THAT'S ALWAYS A PROBLEM, THIS IS AN ISSUE OF PHYSICIANS BEING APPROPRIATELY TRAINED, WHETHER IT'S INTERNISTS, CARDIOLOGISTS OR NEPHROLOGISTS IN THE PROPER SELECTION OF PATIENTS GOING FOR THE PROCEDURE. SO THE PROBLEM HERE IS NOT THE TRAINING OF THE INTERVENTIONALISTS BUT DEVELOPING CLEAR EVIDENCE TO DEFINE WHICH PATIENTS AND BY WHAT CRITERIA PATIENTS SHOULD BE SELECTED.
DR. GARBER: BILL.
DR. LEWIS: AND THE COROLLARY TO THAT IS, THE TIGHTER THE SELECTION CRITERIA ARE, THE LOWER THE NUMBER OF CASES, AND THEREFORE THE HIGHER THE DIFFICULTY OF THE LEARNING CURVE. AND WHEN YOU LOOK AT THE NUMBERS FROM CORAL, CORAL WILL PROBABLY, IF YOU LOOK AT THE NUMBER OF CENTERS AND THE NUMBER OF PATIENTS THEY'RE TRYING TO ENROLL, THE NUMBER OF PATIENTS PER YEAR IS PROBABLY GOING TO BE ABOUT THREE PER YEAR, AND IN DRASTIC THAT NUMBER WAS ACTUALLY ONE PATIENT PER YEAR PER CENTER. SO WHEN WE LOOK AT THE NUMBERS IT'S GOING TO BE IMPORTANT HOW THE STUDIES

DEFINE THEIR CRITERIA. IF IT'S REQUIRED THAT YOU HAVE A 20-MILLIMETER DROP IN A 70 PERCENT LESION, THE NUMBERS OF PATIENTS ARE GOING TO BE MUCH SMALLER THAN WHAT'S BEING CURRENTLY DONE, AND THE OPERATOR CAPABILITY MAY BE VERY, VERY BROAD, THE RANGE OF OPERATOR CAPABILITY MAY BE VERY, VERY BROAD.

DR. GARBER: OKAY, THANK YOU. ANYONE ELSE WANT TO COMMENT ON THAT? OKAY.

NOW THIS ONE IS GOING TO BE POTENTIALLY THE LARGEST OF THESE THREE SUBQUESTIONS. BASED ON THE EVIDENCE PRESENTED, HOW CONFIDENT ARE YOU THAT PUBLISHED RESULTS APPLY TO PATIENT SUBGROUPS NOT REPRESENTED IN THE STUDY POPULATIONS? AND HERE I THINK IT IS REALLY IMPORTANT FOR YOU TO MENTION, IF YOU GIVE A LOW SCORE, WHICH SUBGROUPS YOU BELIEVE WERE NOT WELL REPRESENTED, OKAY? DID YOU WANT TO SAYING ANYTHING? OKAY.

(MEMBERS OF THE PANEL VOTED, RESULTS WHICH WERE RECORDED BY STAFF.)

DR. TEXTOR: I'LL COMMENT ABOUT THAT. I THINK THE ACHILLES HEEL OF THE PUBLISHED PROSPECTIVE TRIALS IS THAT THEY ARE A VERY SMALL AND SELECTIVE GROUP. THE NUMBER OF EXCLUSIONS, AND THAT'S BEEN A PROBLEM, REALLY, IN ALL THE INTERVENTION TRIALS, IS THE PRESUPPOSITION OF PEOPLE REALLY BEING TOO ILL OR

00207

NEEDING THE PROCEDURE TOO MUCH REALLY FORCED THE SELECTION AND WE REALLY CAN'T GAUGE FROM THE PUBLISHED LITERATURES, IT'S ALMOST IMPOSSIBLE TO KNOW EXACTLY WHO THESE INDIVIDUALS WERE. SO I THINK IT'S VERY LIKELY THAT THERE ARE LARGE GROUPS OF PEOPLE FOR WHOM THOSE RESULTS DO NOT APPLY, AND I HAVE NO IDEA WHO THEY ARE.

DR. SCHWARTZ: AND MY PROBLEM WITH THE QUESTION THE WAY IT IS, EVEN FOR THOSE GROUPS WHO ARE INCLUDED IN THE TRIALS, WE DON'T HAVE ADEQUATE POWER AND WE NEVER WILL, BECAUSE THE FEW STUDIES BEING DONE, LIKE CORAL, I ASSUME ARE BEING POWERED NOT FOR SUBGROUP ANALYSIS BUT ARE BEING POWERED FOR A PRIMARY ANALYSIS, AND UNFORTUNATELY WE'RE GOING TO HAVE TO RELY IN THE FORESEEABLE FUTURE ON, YOU KNOW, NONEXPERIMENTAL DATA ANALYSIS.

DR. GARBER: YEAH, I THINK SANDY HAS A VERY IMPORTANT POINT. SO AS I HEAR YOUR POINT, EVEN IF THE GROUP IS REPRESENTED IN TRIALS, THERE MAY BE TOO FEW OF THEM TO BE ABLE TO DRAW CONCLUSIONS ABOUT WHETHER IT WORKS OR HOW IT WORKS.

DR. SCHWARTZ: YEAH. WHAT ARE WE GOING TO KNOW ABOUT PEOPLE WHO HAVE CORONARY DISEASE OR DIABETES, OR, YOU KNOW, UNDERLYING OR INDEPENDENT RENAL DISEASE. WE'RE NOT GOING TO HAVE ENOUGH OF

THOSE PATIENTS IN ORDER TO BE ABLE TO SAY MUCH.
DR. CHARYTAN: BASED ON A LOT OF WHAT WE'VE HEARD TODAY, IT SEEMS TO ME THAT THE CORAL TRIAL IS ALMOST TOO INCLUSIVE, THAT THE PROBLEM IS DOING PROCEDURES ON AN AWFUL LOT OF PATIENTS, AND THE CONSENSUS THAT I TAKE FROM THE DISCUSSION HERE IS THAT IT'S A VERY SELECT SUBGROUP OF PATIENTS WHO PROBABLY MIGHT BENEFIT FROM THE PROCEDURE. AND IF WE'RE GOING TO DO A STUDY THAT INCLUDES A LOT OF PEOPLE, WE'RE ALMOST SETTING OURSELVES UP TO SHOW A NEGATIVE OUTCOME, BECAUSE PERHAPS PEOPLE IMPROVE, BUT BY DEFINITION MAY NOT BENEFIT FROM THE PROCEDURE.
DR. GARBER: WELL, THIS IS A GOOD POINT. THAT MAY BE A STRONG ARGUMENT FOR FIGURING OUT HOW TO GET A LOT MORE PATIENTS INTO CORAL SO THAT IT'S POWERED TO ACTUALLY ANSWER QUESTIONS FOR SUBGROUPS. DID YOU WANT TO SAY SOMETHING?
DR. DWORKIN: IF I CAN SAY SOMETHING ABOUT THAT, IT'S AN OBVIOUS CONUNDRUM WHEN YOU'RE DESIGNING CLINICAL TRIALS IS TO, YOU KNOW, SELECT A POPULATION TO STUDY. I THINK CORAL WAS DESIGNED TO BE INCLUSIVE, AGAIN, BECAUSE THE PERCEPTION OF MANY PEOPLE IN THIS FIELD AND CERTAINLY PEOPLE THAT WROTE THE PROTOCOL, MYSELF INCLUDED, WAS THAT WE WERE UNABLE TO DEFINE A SUBSET OF PATIENTS WITH

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RENOVASCULAR DISEASE FOR WHOM IT WAS CLEAR THAT REVASCULARIZATION PROVIDED BENEFIT. SO I KNOW YOU'VE HEARD PEOPLE TELL YOU TODAY THAT PEOPLE WITH IMPAIRED KIDNEY FUNCTION OR UNCONTROLLED HYPERTENSION OR RECURRENT EPISODES OF PULMONARY EDEMA ARE SUBSETS OF PATIENTS FOR WHOM OUTCOMES ARE BETTER WITH REVASCULARIZATION, BUT WE DIDN'T FEEL THAT THAT WAS ENOUGH, AND SO ALL OF THOSE PATIENTS ARE IN THE TRIAL.

AND I THINK IN DESIGNING THE TRIAL, WE DIDN'T WANT TO EXCLUDE ANY OF THOSE GROUPS BECAUSE THEN WE WOULD STILL HAVE NO EVIDENCE ABOUT THOSE GROUPS. NOW WHETHER WE WILL BE ABLE TO TEASE OUT ALL THESE DIFFERENT SUBGROUPS AT THE END OF THE DAY, I DON'T EXPECT THAT WE WILL BE ABLE TO. WE DO HAVE SOME PREPLANNED SUBGROUP ANALYSES. WE WILL BE LOOKING AT ISSUES LIKE UNILATERAL VERSUS BILATERAL DISEASE, DIABETES, THE IMPACT OF GENDER AND RACE. SO WE DO HAVE SOME PREPLANNED ANALYSES AND WE WILL BE ABLE TO LOOK AT SOME OF THE COMPONENTS OF THE COMPOSITE ENDPOINT INDIVIDUALLY, SO WE WILL PROBABLY HAVE DECENT POWER TO LOOK AT SOMETHING LIKE MORTALITY. BUT YOU KNOW, THERE WILL BE UNANSWERED QUESTIONS CLEARLY.

DR. GARBER: OKAY. DID ANYBODY ELSE WANT

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TO RAISE OR BRING UP ANY OTHER POINTS? THEN WE WILL MOVE ON TO QUESTION 3.

DR. TEXTOR: BEFORE WE LEAVE THAT, COULD I JUST ASK THE QUESTION? I MEAN, PART OF THE PROBLEM THAT STRIKES ME WITH A TRIAL THAT IS HAVING SLOW ENROLLMENT IS THAT YOU REALLY RUN THE RISK OF A MOVING TARGET AND NEVER ACCRUING THE CRITICAL NUMBER OF PEOPLE YOU NEED TO ANSWER THIS QUESTION IN SOME REASONABLE PERIOD OF TIME. WHAT WOULD BE THE ARGUMENT AGAINST REQUIRING ALL PATIENTS TO BE IN A TRIAL SETTING IF THEY'RE GOING TO BE TREATED.

DR. GARBER: STEVE, I THINK THAT'S THE HEART OF OUR DISCUSSION TODAY, AND IF I COULD JUST ASK YOU TO BRING THAT UP AGAIN WHEN WE GET TO QUESTION 4, AND IN FACT WITH 4, WE CAN BRING UP ISSUES OF POWER, WHETHER WE WANT TO KNOW ABOUT SOME SUBGROUPS, AND IS A REGISTRY ADEQUATE, DO WE WANT MORE PEOPLE ENROLLED IN RANDOMIZED TRIALS, SO ON AND SO FORTH. THAT'S GOING TO BE THE HEART OF THE DISCUSSION FOR QUESTION 4, SO WE WILL GET INTO IT VERY SOON HOPEFULLY.

QUESTION 3 -- AND BY THE WAY, I HOPE THAT ALL THE PEOPLE REPRESENTING CORAL WILL REMAIN FOR THAT DISCUSSION, BECAUSE THAT'S GOING TO BE VERY IMPORTANT THERE.

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ALL RIGHT. QUESTION 3. BASED ON THE EVIDENCE PRESENTED FOR PATIENTS WITH ATHEROSCLEROTIC RENAL ARTERY STENOSIS, HOW CONFIDENT ARE YOU THAT COMPARED TO AGGRESSIVE MEDICAL TREATMENT ALONE THERE ARE IMPROVED KEY HEALTH OUTCOMES ATTRIBUTABLE TO THE FOLLOWING CO-INTERVENTIONS? SO THE VOTING IS GOING TO, LET ME JUST SUGGEST WHEN YOU VOTE, IT'S GOING TO BE ONE TO FIVE THAT ONE, YOU'RE NOT CONFIDENT, FIVE, YOU'RE HIGHLY CONFIDENT. AND THEN WE WILL STEP TO A SEPARATE QUESTION IF YOU'RE PRETTY CONFIDENT THAT IT IS HARMFUL, OKAY?

DR. SCHWARTZ: I KNOW I SHOULD HAVE SAID THIS IN THE CONFERENCE CALL A COUPLE WEEKS AGO, BUT I HADN'T READ THROUGH ALL THE MATERIALS AT THAT TIME YET. BUT I DON'T THINK WE SHOULD CHANGE, WE CAN'T CHANGE THE WORDS ON EVERY QUESTION, BUT THE WAY I'M GOING TO BE VOTING ON THIS, IT RELATES TO WHAT YOU WERE SAYING BEFORE. THERE'S A PRESUMPTION IN HERE THAT AGGRESSIVE MEDICAL TREATMENT IS THE BEST TREATMENT. WE DON'T EVEN KNOW IF THAT'S EFFECTIVE FOR RENAL ARTERY STENOSIS PER SE. I FEEL THE WAY WE SHOULD THINK ABOUT THIS IS WHAT'S THE INCREMENTAL BENEFIT OR CLINICAL BENEFIT OF THESE APPROACHES OVER AND ABOVE THE AGGRESSIVE MEDICAL THERAPY THAT PEOPLE ARE GOING TO BE GETTING FOR HYPERTENSION AND

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CARDIOVASCULAR RISK REDUCTION, BUT WITHOUT A PRESUMPTION THAT THESE ARE PARTICULARLY EFFECTIVE IN PEOPLE WITH RENAL ARTERY STENOSIS, BECAUSE I DON'T THINK WE KNOW THAT.

DR. GARBER: I THINK THAT THAT'S A GOOD STATEMENT OF WHAT I UNDERSTAND TO BE THE INTENT OF THE QUESTION. I THINK WHAT SANDY IS SAYING IS, THIS IS AN ISSUE THAT COMES UP NOT INFREQUENTLY, THAT THE COMPARATOR IS SOMETHING ABOUT WHICH WE HAVE VERY LITTLE EVIDENCE. AND WHAT WE'RE BEING ASKED TO VOTE ABOUT IS HOW CONFIDENT ARE WE THAT THIS IS BETTER THAN A COMPARATOR REGARDLESS OF OUR LEVEL OF IGNORANCE ABOUT THE COMPARATOR, THAT THE COMPARATOR IN THIS CASE IS AGGRESSIVE MEDICAL MANAGEMENT OR WHATEVER, IS BETTER THAN PLACEBO.

DR. SCHWARTZ: YEAH. AND I'M NOT THINKING ABOUT THIS AS A COMPARATOR SINCE ALL THESE PEOPLE CLINICALLY SHOULD BE ON THIS OTHER REGIMEN ANYHOW FOR REASONS OTHER THAN KIDNEY FUNCTION OR RENAL ARTERY STENOSIS, JUST BECAUSE THEY HAD ATHEROSCLEROTIC DISEASE. SO I DON'T SEE IT AS A COMPARATOR, I SEE IT AS SORT OF A BASELINE TREATMENT THAT EVERYBODY OUGHT TO BE GETTING.

IT'S SORT OF LIKE IF YOU WANTED TO LOOK AT, WHAT'S THE IMPACT IN A GROUP OF PEOPLE WHO ARE

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GETTING THEIR HYPERTENSION TREATED ARE GETTING SOME SMOKING CESSATION, BEING ON BABY ASPIRIN, BEING ON A BETA BLOCKER, YOU KNOW, WHATEVER THE BASELINE TREATMENT IS.

DR. GARBER: WELL, SANDY, I DON'T WANT TO GET INTO A LENGTHY DISCUSSION WITH YOU, BUT WHEN YOU SAY IMPROVED HEALTH OUTCOMES IT MEANS RELATIVE TO SOMETHING, AND THAT'S THE REASON I USED THE TERM COMPARATOR, WHAT IT'S RELATIVE TO. MARK?

DR. FENDRICK: I WAS FINE UNTIL YOU CONFUSED ME. BECAUSE THE WORD IMPROVED IS IN THE QUESTION, YOU COULD VOTE FOR IT AND SAY IT'S HARMFUL? I DON'T THINK THAT'S CORRECT.

DR. GARBER: NO, NO, NO. THAT WAS ON QUESTION 1 WHERE I --

DR. FENDRICK: I KNOW, BUT YOU JUST SAID --

DR. GARBER: THEN I MISSPOKE. I'M SORRY. I SAID IF IT WAS POSITIVE, YOU COULD VOTE FOR IT. IF IT'S NEGATIVE IN YOUR DISCUSSION. I DIDN'T SAY --

DR. FENDRICK: I MISSED A COMMA THEN. YOU COULD VOTE FOR, AND SAY WHY IT'S NEGATIVE?

DR. GARBER: NO, NO, NO. THIS SAYS IMPROVED. YOU CAN'T VOTE FOR IT.

DR. FENDRICK: OKAY, WE'RE IN AGREEMENT.

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DR. GARBER: SO IF YOU'RE NOT CONFIDENT, IF YOU THINK IT'S HARMFUL, I WOULD GIVE IT A ONE. AND THEN IN EXPLANATION, THAT ACTUALLY IT'S NOT THAT YOU'RE NOT CONFIDENT THAT IT'S BENEFICIAL, BUT IF YOU'RE SURE THAT IT'S NOT, THAT SHOULD COME IN COMMENT, OKAY?

DR. CHARYTAN: JUST AS A QUESTION, AND IT'S A REPETITION, BUT HOW CLEAR WILL IT BE TO THE PEOPLE WHO READ THIS THAT WE'RE VOTING FOR A GROUP AS A WHOLE, BUT THAT MANY OF US MAY FEEL THAT THERE ARE SUBGROUPS IN WHICH THESE THERAPIES MAY BE BENEFICIAL AND IT NEEDS TO BE VIEWED FROM THAT PERSPECTIVE?

DR. GARBER: YOU SHOULD ABSOLUTELY MAKE COMMENTS TO THAT EFFECT IN EXPLAINING YOUR VOTE. AND IT WILL BE A MISUSE OF THE RESULTS OF OUR PROCEEDINGS TODAY IF PEOPLE IGNORE THE COMMENTS. THOSE ARE ABSOLUTELY CRITICAL.

DR. SLAUGHTER: THIS MAY MAKE IT A BIT MORE CONFUSED, BUT I THINK YOU DO HAVE TO COMPARE IT TO MEDICAL THERAPY BECAUSE THE ASSUMPTION HERE IN ALL THE PRESENTATIONS IS THAT RENAL ARTERY STENOSIS, WHETHER DIRECTLY OR THROUGH SOME COMPLEX SYSTEM THAT MAY NOT BE WELL DESCRIBED, IS RESPONSIBLE FOR THE ADVERSE OUTCOMES. SO THEREFORE WHAT WE'RE SAYING IS MEDICAL TREATMENT, YOU KNOW, OF THIS COMPLEX WHICH

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MAY OR MAY NOT BE EXACERBATED BY, OR IS SOLELY RESPONSIBLE FOR THE RENAL ARTERY STENOSIS, EXTENDING THAT IS GOING TO GIVE YOU A BETTER OUTCOME THAN MEDICAL THERAPY, NOT JUST NO TREATMENT. BECAUSE CERTAINLY THERE ARE ADVANTAGES TO ANTIHYPERTENSIVE THERAPY, STATINS, LIPIDS FOR THIS COMPLEX. AND THE ISSUE IS, IS USING A STENT BETTER THAN ORALLY INDUCED MEDICAL THERAPY FOR THIS DISEASE PROCESS THAT RESULTS IN STROKE, KIDNEY FAILURE, HEART ATTACKS AND DEATH.

DR. GARBER: RIGHT, BUT THE ONLY POINT I WANT TO MAKE ABOUT HOW YOU SHOULD VOTE ON THIS IS THE FOLLOWING. YOU ARE ASSUMING THAT THIS IS A COMPARISON OF RAR, STENTING, WHATEVER, TO MEDICAL THERAPY. I DON'T CARE HOW CONFIDENT YOU ARE ABOUT WHETHER MEDICAL THERAPY WORKS. THAT'S NOT THE QUESTION. THE QUESTION IS, IS THIS, ARE YOU CONFIDENT THAT THIS IS BETTER, OR HOW MUCH BETTER THIS IS THAN MEDICAL THERAPY, REGARDLESS OF THE LEVEL OF EVIDENCE, ET CETERA, FOR MEDICAL THERAPY. THAT'S HOW YOU'RE VOTING. IS THIS BETTER? AND IF YOU THINK YOU KNOW IT'S WORSE, GIVE THIS A ONE, AND THEN IN THE COMMENTS EXPLAIN WHY YOU THINK IT'S NOT JUST THIS BETTER BENEFIT, BUT WHY YOU THINK IT'S WORSE. IS EVERYBODY CLEAR WITH THAT? MARK,

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SANDY? OKAY.
SO FIRST WE ARE VOTING ON -- AND I WANT TO MAKE SURE YOUR BALLOTS CORRESPOND TO WHAT WE HAVE HERE. THE FIRST ONE IS SURGICAL RENAL ARTERY RECONSTRUCTION.
(MEMBERS OF THE PANEL VOTED, RESULTS WHICH WERE RECORDED BY STAFF.)
DR. GARBER: DOES ANYBODY WANT TO DISCUSS REASONS FOR THEIR VOTE? THIS ONE I THINK WE HAVE SORT OF ALREADY IMPLIED WHY YOU VOTED THE WAY YOU DID.
DR. KRIST: I'LL PUT A CAVEAT IN MINE. I SAID ONE, BUT AN EXCEPTION MIGHT BE SOMEBODY WHO'S UNDERGOING SURGERY FOR ANOTHER REASON AS WE TALKED ABOUT.
DR. FLAMM: THAT'S WHY I VOTED TWO.
DR. GARBER: OKAY, GREAT.
DR. EDWARDS: I HELD UP TWO CARDS, NOT JUST BECAUSE I'M CRYING FOR ATTENTION, BUT AS TO SURGERY, I WOULD VIEW IT AS A TWO IN REFERENCE TO BEST MEDICAL SECONDARY PREVENTION AT THIS TIME FOR CARDIOVASCULAR EVENTS, BUT I'M UNCERTAIN FOR RENAL FUNCTION.
DR. GARBER: RIGHT. OKAY. PTRA WITHOUT STENT PLACEMENT.

(MEMBERS OF THE PANEL VOTED, RESULTS WHICH WERE RECORDED BY STAFF.)

DR. GARBER: SO THIS IS NOT REALLY WHAT THE QUESTION ASKS EXACTLY BUT IT'S PART OF THE REASON FOR YOUR VOTE. IS EVERYBODY CONVINCED THAT STENTS ARE BETTER THAN PTRA WITHOUT STENTS?

(CHORUS OF AYES.)

DR. GARBER: SO MAYBE THAT'S A MESSAGE THAT CMS NEEDS TO TAKE AWAY FROM THAT. OKAY. C IS STENTING WITH BARE METAL STENTS.

(MEMBERS OF THE PANEL VOTED, RESULTS WHICH WERE RECORDED BY STAFF.)

DR. GARBER: AND NOW IS THE TIME TO LET US KNOW ABOUT ANY SUBGROUPS FOR WHICH YOU WANT TO MAKE A DISTINCT CASE OR DISTINCT REASON FOR VOTING THE WAY YOU DID.

DR. CHARYTAN: WELL, I THINK THIS REALLY NEEDS TO BE EMPHASIZED, PARTICULARLY IF MEDICARE IS GOING TO LOOK AT THIS IN A SUBSEQUENT COVERAGE DECISION THAT THERE IS CLEARLY CLINICAL EVIDENCE OF STANDARD OF PRACTICE, WHICH IS JUST THAT THERE ARE SUBGROUPS OF PATIENTS THAT PROBABLY BENEFIT IF CAREFULLY SELECTED. AND PERHAPS THE OUTCOME THAT WAS GIVEN BY, I DON'T REMEMBER THE NAME OF THE GENTLEMAN WHO IS AT THE BACK OF THE ROOM, MIGHT BE ENOUGH ON

THOSE SITUATIONS WITH BILATERAL RENAL ARTERY STENOSIS, UNILATERAL RENAL ARTERY STENOSIS, AND PATIENTS WITH DEMONSTRATED RECURRENT PULMONARY EDEMA IN A SETTING OF RENAL ARTERY STENOSIS AND REDUCED KIDNEY FUNCTION. AND PERHAPS VERY WELL TREATED PATIENTS WHO DESPITE WELL PROVEN THERAPY DO NOT RESPOND AND HAVE EVIDENCE OF RENAL ARTERY DISEASE, AGAIN, VERY WELL SELECTED. BUT THERE ARE SUBGROUPS WHO WILL BENEFIT AND THOSE NEED TO BE IDENTIFIED.

DR. GARBER: ANY OTHER COMMENTS?

DR. LEWIS: DR. DWORKIN'S COMMENTS ASIDE, THE ISSUE IS GOING TO BE THAT THERE ARE CERTAIN PATIENTS THAT ARE REALLY NOT GOING TO QUALIFY, AND I'M THINKING IF FLASH PULMONARY EDEMA OR CARDIOVASCULAR HEART DISEASE CANNOT BE CONTROLLED, AND IT'S CLEAR THAT THIS IS RELATED. AND I THINK IT'S DIFFICULT TO GO AGAINST, YOU KNOW, THE LIMITED DATA THAT'S OUT THERE SAYING WE REALLY SHOULD EXCLUDE THOSE PATIENTS FROM THIS THERAPY.

DR. GARBER: SANDY?

DR. SCHWARTZ: I'M SURE THAT AT LEAST HALF THE PEOPLE, OR PERHAPS EVERYBODY IS THINKING THE SAME THING, BUT JUST TO GET IT ON THE RECORD, I THINK THAT EVEN IF THERE IS A LEVEL OF UNCERTAINTY, THE ALTERNATIVE TO USING THE INTERVENTION FOR THE

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UNDERLYING RISK IS WITHOUT USING THE INTERVENTION. SO IF SOMEBODY, THERE MAY NOT BE REAL GOOD DATA ON UNCONTROLLED HYPERTENSION, BUT IF EVERYTHING YOU'RE DOING IS NOT WORKING AND WE KNOW WHAT'S THERE IS BAD, SO I THINK WHATEVER MEDICARE DOES, I THINK WE NEED TO INFORM THAT EVEN IF THERE IS A GENERAL CONSENSUS, THERE STILL ALWAYS NEEDS TO BE A STRONG EXCEPTION POLICY FOR PATIENTS WHO WE KNOW ARE GOING TO DO POORLY IN THE ABSENCE OF IT. IN OTHER WORDS, TAKING ON THE RISK IS WORTH IT IN THOSE SITUATIONS.

DR. GARBER: MIKE.

MR. LACEY: I JUST WANTED TO REEMPHASIZE WHAT I THOUGHT WAS A VERY POWERFUL (INAUDIBLE) TOTALITY OF THE EVIDENCE TO DATE. IT SEEMS THERE WAS A VERY STRONG SYSTEM TREND IN THESE OUTCOMES THAT ARE BEING MEASURED. AND I DIDN'T VOTE FIVE, BUT I VOTED FOUR BECAUSE I DEFINITELY THINK THAT, BASED ON THIS DISCUSSION, ADDITIONAL DATA NEEDS TO BE COLLECTED IN ALL THE AREAS.

AND I JUST HOPED TO BRING UP ONE OTHER POINT, THAT IN THE CASE OF THREE OR FOUR-DRUG THERAPY, WE ALSO HAVE TO THINK ABOUT COMPLIANCE. AND I THINK THERE WAS A MENTION OF IT, BUT NOT REALLY ANY DISCUSSION ABOUT IT, AS WELL AS THE BURDEN OF COST TO THE PATIENT AND THE COST EFFECTIVENESS AS IT RELATES

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TO MEDICARE. SO I THINK IT HAS A ROLE THERE AND WHEN WE THINK ABOUT THE OVERALL COVERAGE AND THE ABILITY FOR THE AVERAGE POPULATION TO ACHIEVE THE AGGRESSIVE MEDICAL MANAGEMENT, THAT IS ALSO A BIG CHALLENGE IN TERMS OF COMPLIANCE.

DR. GARBER: LET THE RECORD REFLECT THAT ONLY THE INDUSTRY REPRESENTATIVE REFERRED TO COST.

MR. LACEY: I'M AN ECONOMIST.

DR. SCHWARTZ: THE OTHER THING THAT WAS REALLY DRIVEN HOME BY THE FIRST PRESENTATION TODAY, AND THIS IS NOT A CRITICISM OF THE PRESENTATION, BUT IT'S AN UNDERSCORING OF THE NEED TO GET PEOPLE INTO TRIALS QUICKLY AND TO GET THESE ANSWERS QUICKLY. ONE OF THE CRITICISMS THAT'S OFTEN MADE, AND AS YOU KNOW, WHEN WE SIT ON TECS, WHAT WE OFTEN HEAR IS COMPARED TO THIS TRIAL THING OR THAT, BUT THE RANDOMIZED TRIALS THAT WERE TALKED ABOUT TODAY WERE PUBLISHED IN 1998, WHICH MEANS THEY WERE COMPLETED IN '96 OR '97, WHICH MEANT THEY WERE DESIGNED IN '90 OR '92, AND THERE WAS NO EVIDENCE AT THAT TIME THAT STATINS -- STATINS WERE JUST BEING TESTED AT THAT POINT. AND YOU KNOW, FOR ACE INHIBITORS, THE EVIDENCE WAS STILL ACCUMULATING.

SO IN THIS PARTICULAR SITUATION IT DOESN'T BOTHER ME AS MUCH AS IT WOULD IN GENERAL AND I THINK

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IT WILL IN THE FUTURE, BECAUSE THE ORIGINAL STUDIES, ESPECIALLY CLINICAL TRIALS, WERE MORE CONVINCING IN TERMS OF THE EFFECTIVENESS OF THE INTERVENTION. BUT IT DOES RAISE THE ISSUE, PARTICULARLY WITH DEVICES, OR WITH ANYTHING, IT GETS BACK TO THE BASELINE, WHAT'S THE COMPARATOR TREATMENT? AND WE'RE ALWAYS GOING TO BE, BY THE TIME CORAL COMES OUT, WE'RE GOING TO BE EXPECTING IT TO, WE'RE GOING TO SAY WELL, IT DIDN'T COMPARE IT TO SOMETHING THAT JUST COMES OUT IN A JOURNAL IN THE NEXT TWO WEEKS.

SO WE'RE ALWAYS GOING TO SORT OF BE BEHIND THE EIGHT BALL AND I THINK WE NEED TO FIGURE OUT, AND I DON'T HAVE A GOOD ANSWER, BUT I THINK WE NEED TO FIGURE OUT HOW TO BUILD THAT IN TO MAKE SURE WE'RE PRACTICING STATE OF THE ART MEDICINE AND OUR POLICIES REFLECT THAT, BUT ALSO RECOGNIZING THE REALITY THAT WE'RE ALWAYS LAGGING.

DR. GARBER: YEAH, BARRY.

DR. PRESSMAN: I THINK MOST OF US VOTED THREE, AND I DON'T KNOW WHAT THE OTHER PEOPLE'S INDICATIONS FOR THAT WERE, BUT MY VOTE WASN'T TO SAY THAT I DON'T BELIEVE STENTS ARE VALUABLE. MY VOTE SHOULDN'T BE USED BY CMS TO DENY STENTS IN PATIENTS WHO FAIL MEDICAL THERAPY FOR THE MOMENT. IT'S ONLY TO SAY THAT I THINK WE NEED MORE DATA TO FIND OUT,

BUT IN THE MEANTIME IT'S UNCERTAIN, AND BEING UNCERTAIN, I THINK CMS HAS TO ACT AS THOUGH THEY DON'T KNOW AND BE VERY, VERY CAREFUL ABOUT WHAT THEY DO AND DON'T PAY FOR GOING FORWARD UNTIL WE HAVE THE ANSWERS. BECAUSE IF THEY DON'T PAY FOR IT, THEY'VE ALREADY DECIDED IT'S CERTAIN.

DR. GARBER: THAT'S ACTUALLY NOT MY UNDERSTANDING. IF THEY DON'T PAY FOR IT, THEY MAY DO THAT BECAUSE IT'S UNCERTAIN, BUT THIS AGAIN IS SOMETHING THAT SHOULD BE TALKED ABOUT IN THE CONTEXT OF QUESTION 4.

DR. EDWARDS: I WOULD JUST LIKE TO VERIFY THAT I VOTED AGAIN WITH TWO, THREE FOR CARDIOVASCULAR AND FOUR FOR RENAL FUNCTION. BUT I WANT TO BE CERTAIN THAT, A, WE ALL THANK THE PEOPLE WHO SET UP CORAL, BECAUSE EVEN THOUGH I WOULD SAY IT'S FOUR FOR RENAL FUNCTION, THAT'S BASED ON MY DIGEST OF THE LITERATURE AND MY RELATIVE KNOWLEDGE OF THE PRACTICE IN RENAL DISEASE. BUT I CERTAINLY FEEL THAT THERE IS -- I MEAN, I WOULD CERTAINLY HAVE CLINICAL EQUIPOISE IN PUTTING PATIENTS INTO TRIALS SUCH AS CORAL, AND IT IS CRITICALLY IMPORTANT THAT IF THERE ARE ANY MEASURES WE CAN TAKE TO MAKE THEIR ENROLLMENT MORE ROBUST TO ALLOW FOR THE SECONDARY ANALYSIS OF ALL THESE GROUPS THAT WE HAVE MENTIONED, AND I THINK

THAT HAS TREMENDOUS MERIT.
(DR. GARBER AND DR. SALIVE CONFERRED OFF THE RECORD.)
DR. GARBER: OKAY, THANK YOU. I JUST WANTED TO ASK THE PANEL THIS, WHAT I WAS ASKING MARCEL ABOUT. FOR 3.B, IT'S ABOUT THE DRUG-ELUTING STENTS AND THE PANEL UNANIMOUSLY GAVE THAT A ONE. YOU DON'T HAVE TO VOTE ON HOW EFFECTIVE YOU THINK IT IS IF ALL OF YOU THINK THERE IS NO EVIDENCE AT ALL. SO WOULD YOU BE COMFORTABLE JUST SAYING THERE'S NO EVIDENCE ON WHICH TO MAKE A DETERMINATION?
(CHORUS OF AYES.)
DR. GARBER: DOES ANYBODY DISAGREE THEN?
(NO RESPONSE.)
DR. GARBER: OKAY. SO QUESTION 4, YOU HAVE ALL BEEN CHOMPING AT THE BIT FOR THIS ONE. AND LET ME ADD, I THINK MARK ALLUDED TO THIS, THIS IS CALLED THE MEDICARE EVIDENCE DEVELOPMENT AND COVERAGE ADVISORY COMMITTEE. THE REASON FOR THE CHANGE IN ITS NAME, THE ADDING OF EVIDENCE DEVELOPMENT IS NOT JUST SAYING THE EVIDENCE ISN'T ADEQUATE AND NOT ONLY SAYING THERE HAVE TO BE MORE STUDIES, BUT TO ACTUALLY BE ABLE TO DO SOMETHING MORE ACTIVE IN TERMS OF MAKING SURE EVIDENCE GETS COLLECTED, SO WE CAN ASK QUESTIONS LIKE THE FIRST THREE QUESTIONS TODAY WITH A

BETTER EVIDENCE BASE.
SO THIS IS YOUR CHANCE TO TALK ABOUT, ARE THERE SOME CIRCUMSTANCES OR ARE THERE WAYS THAT WE MIGHT THINK ABOUT USING MEDICARE COVERAGE POLICY TO ENCOURAGE THE DEVELOPMENT OF MORE EVIDENCE, WHETHER IT'S RANDOMIZED TRIALS, REGISTRIES, OR SOME OTHER MECHANISM ALTOGETHER. BARRY, DID YOU WANT TO MAKE A COMMENT?
DR. PRESSMAN: NOT SPECIFICALLY TO THIS QUESTION, NOT THE ONE YOU JUST RAISED.
DR. GARBER: WELL, THAT WAS A LEAD-IN TO THIS QUESTION, WHICH IS, SHOULD MEDICARE NATIONAL COVERAGE OF ANY NON-MEDICAL TREATMENTS FOR ATHEROSCLEROTIC RENAL ARTERY STENOSIS BE LIMITED ONLY TO PATIENTS ENROLLED IN QUALIFIED CLINICAL RESEARCH STUDIES? BUT THAT PART OF IT IS GOING TO BE, WHAT DO YOU MEAN BY A QUALIFIED CLINICAL RESEARCH STUDY. SO YOU MIGHT SAY I DON'T THINK THEY HAVE TO BE ENROLLED IN A RANDOMIZED TRIAL BUT THEY HAVE TO BE IN SOME KIND OF REGISTRY, SOME KIND OF NATIONAL REGISTRY. YOU MIGHT SAY IT SHOULD BE PROVIDED FOR EVERYBODY WHO WANTS IT BUT YOU'D LIKE, OF COURSE, CORAL TO GO FORWARD. OR YOU MIGHT SAY THERE SHOULD BE INCENTIVES TO GET MORE PATIENTS INVOLVED IN CORAL AND THESE RANDOMIZED TRIALS.

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SO THERE'S A WHOLE SERIES OF OPTIONS YOU MIGHT COME UP WITH TO ANSWER THIS QUESTION, BUT PART OF IT IS YES-NO, SHOULD THERE BE SOME RESTRICTIONS ON PEOPLE ENROLLED IN STUDIES. BUT IF YOU THINK THERE SHOULD BE SOME INCENTIVE TO ENROLLMENT IN STUDIES, THEN YOU SHOULD SAY SOMETHING ABOUT WHAT KIND OF STUDY YOU HAVE IN MIND, WHAT THE SPECIFIC DETAILS ARE, OKAY? GO AHEAD, BARRY.

DR. PRESSMAN: I WOULD LIKE TO REFER BACK TO A QUESTION THAT I ASKED DR. MURPHY EARLIER, AND I THINK HE RESPONDED TO IT. I ASKED HIM FOR THIS SPECIFIC PURPOSE, BECAUSE I DO BELIEVE IT'S VERY IMPORTANT THAT WE MAKE THIS AVAILABLE TO PATIENTS WITH SOME CRITERIA, AND THOSE CRITERIA OUGHT TO BE AT LEAST SOME OF THE ONES HE MENTIONED, INCLUDING TWO OR THREE MONTHS OF FAILED MEDICAL THERAPY, SO IT'S NOT JUST THAT EVERY PATIENT WHO COMES IN WITH RENAL ARTERY STENOSIS, WHETHER OR NOT THEY HAVE HYPERTENSION, IS TREATED. AND NONE OF THESE WILL BE WHAT WE CALL AT MY HOSPITAL DRIVE-BYS, THEY HAPPEN TO BE THERE FOR ANOTHER PROCEDURE, YOU NOTICE RENAL ARTERY STENOSIS IS THERE, AND YOU FIX IT ON THE WAY. WE WANT TO PREVENT THOSE KIND OF TREATMENTS BUT WHAT WE WANT TO DO, I THINK, IS MAKE IT AVAILABLE TO PATIENTS WHO AT LEAST IN SOME OF THE

CATEGORIES HAVE SEVERAL MONTHS OF FAILED ADEQUATE THERAPY, THEY HAVE TO HAVE A CERTAIN DEGREE OF STENOSIS, THEY SHOULD HAVE A GRADIENT. AND THERE ARE OTHER CRITERIA THAT THE CLINICIANS MAY COME UP WITH THAT I'M MISSING HERE, BUT I WOULD LIKE TO BE SURE THAT WE MAKE IT AVAILABLE. AND FOR THE REGISTRY, I WOULD LIKE TO MAKE SURE WE ARE GETTING SOMETHING FOR IT, THAT WE'RE LEARNING SOMETHING AT THE SAME TIME.

DR. GARBER: SO BARRY, YOU'RE SAYING EVERYBODY SHOULD HAVE TO ENROLL IN THE REGISTRY EVEN IF THEY HAVE THOSE CHARACTERISTICS, OR JUST PEOPLE WHO DON'T FIT IN THOSE CATEGORIES?

DR. PRESSMAN: I'M SAYING IT SHOULDN'T BE DONE AT ALL IF YOU DON'T HAVE THE CHARACTERISTICS AND EVERYBODY WHO'S DONE SHOULD BE IN THE REGISTRY.

DR. GARBER: OKAY, GOT IT. THANKS. YEAH, MARK?

DR. SLAUGHTER: WHAT CONCERNED ME A LOT IS AS THEY SHOWED OVER THE YEARS, A FAIRLY BRIEF TIME PERIOD, IT HAS GONE FROM 7,000 TO 18,000, THEN UP TO 35 TO 40,000 PROCEDURES. AND THE FACT OF THE MATTER IS, THE CORAL STUDY IS AT A HUNDRED WONDERFUL INSTITUTIONS THAT I'M CERTAIN ARE BUSY. SO THE QUESTION IS, IF THERE'S 30,000 A YEAR BEING DONE NOW, THE QUESTION IS WHY CAN'T THEY GET A THOUSAND

PATIENTS WITHIN A YEAR. AND THE ISSUE IS, MOST OF THESE PATIENTS ARE BEING DONE MOST LIKELY IN INSTITUTIONS WITHOUT A LOT OF RIGOR AND OVERSIGHT. AND THIS ALL GREW WHEN THERE WAS LITTLE OR AT LEAST EQUIVOCAL DATA. I DO THINK IT IS VERY DIFFICULT TO ENROLL PATIENTS IN RANDOMIZED TRIALS, AND I'VE PARTICIPATED IN NUMEROUS ONES, FOR VARIOUS REASONS, FINANCIAL BEING ONE, WHICH IS UNFORTUNATELY TRUE. SO I DO THINK THERE'S A LOT OF VALUE IN A MANDATED REGISTRY AND I DO NOT THINK IT'S UNREASONABLE IF YOU HAVE A MANDATED REGISTRY WITH SET DATA POINTS THAT SAY, YOU KNOW, A FIVE-PAGE CASE REPORT HAS TO BE FILLED OUT PRIOR TO DOING THE PROCEDURE. SO WITHIN TWO YEARS, YOU WOULD HAVE 60,000 PATIENTS AND YOU WOULD BE ABLE TO ANSWER A LOT OF THESE SUBSETS, AND YOU WOULD AT LEAST HAVE A HUGE START.

SO I AGREE, PATIENTS SHOULD STILL HAVE ACCESS TO IT. I THINK THE CURRENT DATA IS CERTAINLY EQUIVOCAL, BUT IT'S CERTAINLY PROMISING. AND I THINK A REGISTRY WOULD BE ONE APPROACH, AS WELL AS ONGOING INDIVIDUAL RANDOMIZED TRIALS FOR SPECIFIC SUBSETS.

DR. GARBER: BILL MAISEL, I THINK YOU WERE NEXT.

DR. MAISEL: I WAS JUST LOOKING FOR A

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LITTLE BIT OF CLARIFICATION ON THE QUESTION AND WHAT THE MEANING OF ANY WAS, BECAUSE I COULD READ THE QUESTION AS, SHOULD MEDICARE NATIONAL COVERAGE OF SOME NON-MEDICAL TREATMENTS FOR ATHEROSCLEROSIS BE LIMITED, OR IT COULD BE COVERAGE OF ALL NON-MEDICAL TREATMENTS. SO I'M WITH THE PANEL, MEANING I FIND SOME GROUPS THAT I DEFINITELY FEEL SHOULD BE ENROLLED, AND SOME THAT I DEFINITELY FEEL DO NOT NEED TO BE ENROLLED, BUT I'M JUST HAVING TROUBLE INTERPRETING THE ACTUAL QUESTION.

DR. GARBER: I THINK IT'S ANY OF THE FOUR NON-MEDICAL TREATMENTS THAT WE DISCUSSED TODAY IS WHAT'S MEANT BY THE QUESTION.

(INAUDIBLE COLLOQUY BY PANELISTS.)

DR. SCHWARTZ: AS PART OF THE DISCUSSION, I MEAN, I THINK EVERY SPEAKER TODAY SAID THERE'S NO REASON FOR DOING THIS, WE'RE LOOKING AT A PREVENTIVE OR PRESUMPTIVE BASIS, BUT JUST BECAUSE SOMEBODY IS FOUND TO HAVE SOME RENAL ARTERY STENOSIS, THAT DOESN'T MEAN THEY WILL GET THE INTERVENTION, AND I THINK THAT'S THE QUESTION. I THINK EVEN WITHIN THE CONSTRAINT OF SORT OF A TAINTED RETURN FOR DATA COLLECTION, I THINK THERE STILL NEEDS TO BE, OR THERE IS THE OPPORTUNITY FOR INDICATIONS OF NONINDICATIONS. AND THAT MAY SOUND SO OBVIOUS, BUT THE

FACT IS THERE IS THIS VERY LARGE INCREASE IN THE RATE OF PROCEDURES IN THE TOTAL ABSENCE OF ANY SUPPORTIVE DATA. YOU KNOW, IT ISN'T LIKE THERE WAS A NEW STUDY THAT CAME OUT OR ANYTHING LIKE THAT. AND WHILE WE'RE COLLECTING THE DATA, I THINK WE REALLY NEED TO BE CONCERNED ABOUT GROSSLY INAPPROPRIATE USE OF THIS PROCEDURE, INAPPROPRIATE USE, OR WHATEVER ADJECTIVE YOU WANT TO PUT THERE.

DR. GARBER: LET ME JUST ASK SOMETHING.

BARRY HAD SAID EVERYBODY THAT GETS PROCEDURES SHOULD BE IN THE REGISTRY AND THE PROCEDURES SHOULD BE LIMITED TO CERTAIN INDICATIONS. YOU MAY SAY INSTEAD, PEOPLE WITH CERTAIN INDICATIONS NEED TO BE IN A REGISTRY, PEOPLE WITH OTHER INDICATIONS DON'T NEED TO BE IN A REGISTRY AT ALL, THERE NEEDS TO BE NO DATA COLLECTION. AND THE FIRST QUESTION IS, ARE THERE SOME GROUPS FOR WHOM YOU FEEL CONFIDENT THERE NEEDS TO BE NO DATA COLLECTION WHATSOEVER. THAT SORT OF CONTRADICTS THE VOTES ON QUESTION 1.

AND THEN YOU MAY SAY THAT THERE ARE DIFFERENT DATA COLLECTION EFFORTS FOR DIFFERENT TYPES OF PATIENTS WITH DIFFERENT INDICATIONS. SO MAYBE WE'LL SWITCH THE VOTING QUESTION IF IT EMERGES THAT THERE IS SOME CONSENSUS THAT YOU NEED DIFFERENT REQUIREMENTS FOR DIFFERENT POPULATIONS.

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CHAIM, OR MARCEL?
DR. SALIVE: I WANTED TO RESPOND TO THE QUESTION ABOUT THE WORD ANY. I WOULD READ THE WORD ANY TO MEAN NOT ALL, BUT TO MEAN SELECTIVELY ANY OF THESE. SO IF YOU THOUGHT ONLY ONE OF THEM SHOULD BE LIMITED TO A STUDY, SPECIFICALLY STENTING WITH A BARE METAL STENT, THAT WOULD BE IN THIS REALM. IT DOES NOT MEAN ALL.
DR. SCHWARTZ: SHOULD WE JUST GET RID OF THE WORD ANY?
DR. SALIVE: PROBABLY.
DR. GARBER: I THINK IT'S IMMATERIAL BECAUSE IF YOU THINK THERE IS AN ISSUE FOR A PARTICULAR APPROACH, YOU NEED TO SAY WHAT THAT IS AND NOT WORRY ABOUT WHETHER IT'S SOME OR ALL OR WHAT. WE NEED TO KNOW WHAT IT IS.
DR. SALIVE: AND THE DISCUSSION IS THE IMPORTANT PART.
DR. GARBER: CHAIM.
DR. CHARYTAN: FIRST OF ALL, THE QUESTION ABOUT THE REGISTRY, IT SAYS WHETHER COVERAGE SHOULD BE EXTENDED ONLY TO PATIENTS IN A STUDY. NOW IF WE'RE GOING TO CHANGE THE QUESTION THEN, THAT'S A DIFFERENT ISSUE, BUT IF THE QUESTION STANDS, THEN I HAVE SEVERAL COMMENTS THAT I WOULD LIKE TO MAKE.

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FIRST OF ALL, THE WORD WAS USED BEFORE THAT THIS IS AN UNPROVEN THERAPY, AND I THINK THAT MAY BE A MISAPPLICATION OF THE WORD. THE LUNG REDUCTION THERAPY WHEN IT WAS DEALT WITH BY CMS ON A PANEL, A SIMILAR PANEL, WAS AN UNPROVEN THERAPY. THIS IS A THERAPY THAT HAS BEEN USED FOR MANY YEARS BY MANY DISCIPLINES, AND PERHAPS IT HAS BEEN OVERUSED, BUT THERE'S A CLEAR RECOGNITION STATED TODAY AND OVER THE YEARS THAT IT HAS BENEFITS. AND WHAT'S NEEDED IS SOME KIND OF GUIDELINES OR A BETTER CRITERIA FOR DEFINING IT, RATHER THAN FOR PROVING THE THERAPY AS A WHOLE.

SO I DON'T THINK IT SHOULD QUALIFY AS UNPROVEN, YOU KNOW, BE DEFINED AS UNPROVEN THERAPY; RATHER ONE THAT NEEDS TO HAVE A BETTER DEFINITION OF WHEN IT SHOULD BE USED. AND IF WE'RE GOING TO VOTE ON MEDICARE RESTRICTING COVERAGE, IT SHOULD NOT BE RESTRICTING COVERAGE TO STUDIES, BUT RESTRICTING COVERAGE TO CERTAIN CRITERIA THAT PERHAPS CAN BE SET UP BY AN APPROPRIATE PANEL OR GROUP.

SECONDLY, BE VERY CAREFUL. YOU KNOW, WHEN YOU WISH FOR SOMETHING YOU MAY GET IT AND THEN THAT'S NOT WHAT YOU WANT. WE ARE TALKING ABOUT SETTING A POTENTIALLY VERY SERIOUS PRECEDENT OVER HERE. MEDICARE COVERS PROCEDURES THAT HAVE BEEN ACCEPTED

AND FOLLOW A CERTAIN STANDARD OF PRACTICE. IN RARE EXCEPTIONS FOR UNPROVEN THERAPIES AND NEW THERAPIES IT MAY REQUIRE A STUDY FIRST. BUT THIS IS NOT THE SAME SITUATION, AND I THINK WE SHOULD BE VERY CAREFUL ABOUT SETTING A PRECEDENT THAT MAY BE INAPPROPRIATE AND MIGHT CREATE ISSUES, AND MIGHT CARRY OVER TO OTHER AREAS.

SETTING GUIDELINES AND SETTING RESTRICTIONS UNDER WHICH CIRCUMSTANCES A THERAPY IS COVERED IS ONE ISSUE. SAYING THAT A THERAPY SHOULD BE COVERED ONLY AS PART OF A STUDY OR USING MEDICARE AS A WAY TO PUSH PEOPLE INTO A STUDY MAY NOT BE THE APPROPRIATE WAY TO GO, AND I WOULD ARGUE VERY STRONGLY IT IS NOT THE APPROPRIATE WAY TO GO AND THAT THE QUESTION AS RAISED SHOULD NOT BE SUPPORTED BY US, BECAUSE OF THE RISKS OF SETTING A PRECEDENT THAT POTENTIALLY MAY HAVE MANY, MANY BAD CONSEQUENCES.

DR. GARBER: CAROLE, THEN SANDY, THEN MIKE, THEN STEVE.

DR. FLAMM: I JUST WANTED TO ADD COMMENTS TO THE OTHER COMMENTS ABOUT THE SUPPORT OF BOTH PROMOTING ENROLLMENT IN THE ONGOING CLINICAL TRIAL, CORAL, BUT ALSO OFFERING OTHER INFRASTRUCTURE TO GATHER EVIDENCE.

ALONG THE LINES OF THE REGISTRY, I THINK

WE NEED TO ASK OURSELVES WHETHER THIS REGISTRY WILL BE MULTIPLE PROCEDURES IN ONE REGISTRY, OR A SINGLE PROCEDURE, AND THINK ABOUT THOSE KINDS OF OPPORTUNITIES OF COMPARISONS.

I WOULD LIKE TO RAISE A QUESTION ALSO ABOUT WHETHER THERE ARE, WHEN THEY'RE IN A NARROWLY DEFINED CLINICAL SUBSET WHERE THERE MIGHT BE ACUTE CLINICAL INDICATIONS THAT ARE COMPELLING REASONS FOR WANTING TO DO THIS, IF WE SET UP AN INFRASTRUCTURE THAT REQUIRES PARTICIPATION IN A REGISTRY IN ORDER TO BE ABLE TO DO IT AND GET PAID BY MEDICARE, THERE COULD BE BARRIERS FOR PATIENTS WHO MIGHT, AND I WOULD REALLY ASK THE CLINICIANS TO ANSWER THAT QUESTION, WHETHER THAT'S A NARROWLY DEFINED PATIENT POPULATION, THAT MIGHT RECEIVE THE PROCEDURE IN AN ACUTE SETTING EVEN OUTSIDE THE REGISTRY.

DR. GARBER: SANDY.

DR. SCHWARTZ: A COUPLE THINGS. FIRST A QUESTION FOR YOU OR MARCEL OR SOMEBODY FROM CMS. WHAT'S A QUALIFIED CLINICAL RESEARCH STUDY? ARE THERE METHODS FOR DETERMINING WHAT QUALIFIED MEANS? WHO DOES THAT? CAN I DO THAT, OR WAS THIS SOMETHING THAT MEDICARE, CMS WOULD HAVE TO DO, SET UP A MECHANISM TO DO?

DR. SALIVE: WELL, I THINK THE REFERENCE

HERE IS TO OUR CLINICAL TRIALS POLICY, AND THERE IS IN THAT POLICY A PROCEDURE FOR QUALIFYING CLINICAL TRIALS.

DR. SCHWARTZ: SO CMS HAS A PROCEDURE WHEREBY SOMEBODY COULD SUBMIT A CLINICAL TRIAL AND HAVE SOMEBODY EVALUATE IT AND DETERMINE WHETHER THEY WERE QUALIFIED?

DR. SALIVE: RIGHT. AND I WILL ALSO SAY THAT IN OUR GUIDANCE ON COVERAGE AND EVIDENCE DEVELOPMENT, THAT DISCUSSES BOTH CLINICAL TRIALS AND THE USE OF REGISTRIES IN THAT ARENA. SO I THINK WE'RE TRYING TO GET AT THAT IN THIS QUESTION, IT'S NOT NARROWLY FOCUSED. I MEAN, WE DON'T DISTINGUISH AT CMS BETWEEN A STUDY AND REGISTRY, THOSE ARE BOTH, I THINK, TOGETHER IN THIS QUESTION.

DR. GARBER: ONE POINT ABOUT THAT, THOUGH, ALTHOUGH IT'S NOT INCORRECT, HHS HAS NOT ISSUED ITS NEW CLINICAL TRIAL POLICY, HAS IT, AS OF YET? SO WE DON'T KNOW EXACTLY WHAT IT MEANS TO BE QUALIFIED AT THIS POINT IN TIME.

DR. SALIVE: NO, IT EXISTS, AND THE 2000 POLICY WAS UPDATED LAST WEEK WITH SOME LANGUAGE, AND THERE IS A POSSIBILITY IT WILL CHANGE IN THE FUTURE THROUGH A NATIONAL COVERAGE DECISION. I THINK THAT'S UNDER DISCUSSION.

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DR. SCHWARTZ: SECOND, I WOULD LIKE TO PUT A LITTLE BIT MORE IN TO SUPPORT WHAT HAS ALREADY BEEN SAID. MARK FENDRICK AND I WERE BOTH PRINCIPALS IN THE LUNG VOLUME REDUCTION SURGERY, AND IN FACT WE FACED THE EXACT SAME SITUATION. THE SURGEONS AT THE TIME FELT THAT IT WAS FRUITFUL. WE HAD A HELL OF A TIME ENROLLING PATIENTS IN THAT TRIAL, IT TOOK FOREVER, AND CERTAIN SITES I THINK EVEN HAD TO BE DROPPED, BECAUSE SO FEW OF THEIR SURGICAL PATIENTS WOULD BE ENROLLED.

SO I THINK A LOT OF THIS SORT OF DEPENDS ON SORT OF WHERE YOU SIT. BUT THE MOST IMPORTANT THINGS SAID ABOUT CORAL TODAY, I AGREE WITH IT. BUT THE PRECEDENCE OF THIS IS VERY, VERY IMPORTANT, AND I WISH BERNIE WERE HERE, BUT I THINK THIS IS A LITTLE MORE COMPLICATED ETHICALLY FOR A PROCEDURE THAT'S BEEN OUT THERE AND BEING USED, AND, YOU KNOW, I'VE JUST EXHAUSTED MY KNOWLEDGE OF BIOMEDICAL ETHICS HERE, ALTHOUGH I DID WATCH THE TAPE. BUT I THINK DEPENDING ON HOW IT'S STRUCTURED, PARTICULARLY FOR PROCEDURES OR SERVICES THAT ARE ALREADY IN SERVICE, IN SOME ASPECTS SOME ETHICIST MAY TAKE ISSUE WITH THE COERCIVE ASPECT OF THIS.

WHICH LEADS ME TO THE THIRD QUESTION WHICH IS FOR THE CORAL INVESTIGATORS, AND I MEAN, ALL OF US

HAVE BEEN INVOLVED IN CLINICAL TRIALS WHERE EVERYTHING'S A STRUGGLE AND WE ALL HAVE THE SAME ISSUES. I JUST WONDER IF YOU HAVE ANY SENSE OF WHY IT'S SO DIFFICULT. I MEAN, YOU COULD ASK ME ABOUT TRIALS I'VE BEEN INVOLVED IN ON DIFFERENT OCCASIONS, BUT WHY HAS THIS BEEN SO DIFFICULT, WHAT HAVE THE BARRIERS BEEN? BECAUSE IF THE BARRIER IS PRIMARILY FINANCIAL, WHICH IS ALMOST A PRESUMPTION ON PART OF THIS QUESTION, THEN A REGISTRY ISN'T GOING TO SOLVE -- AND I'M NOT A BIG -- I'M A BELIEVER IN MYSELF AND I'M A BIG BELIEVER IN OBSERVATIONAL DATA WHEN IT'S ANALYZED PROPERLY FROM QUASI-NON-EXPERIMENTAL DATA.

BUT I THINK IT'S IMPORTANT FOR US TO UNDERSTAND IN THE CONTEXT OF THIS QUESTION WHERE THE BARRIERS TO ENROLLMENT HAVE BEEN. IS IT THAT PRACTITIONERS JUST BELIEVE THERE IS GOOD, IS THERE A HUGE FINANCIAL INCENTIVE FOR PEOPLE DOING THIS? DO THE PATIENTS REALLY HAVE, ONCE THEY HEAR ABOUT THEY HAVE AN OPTION, DO THEY WANT THIS OPTION? DO YOU HAVE A SENSE OF THAT?

DR. GARBER: MAYBE YOU COULD ALSO ADD, WHAT COULD CMS DO TO HELP INCREASE ENROLLMENT.

DR. COOPER: THIS IS CHRIS COOPER, THE PI OF THE CORAL TRIAL. TO SOME EXTENT, MY PREFERENCE

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WOULD BE TO DEFER TO STEVE TEXTOR AND DR. ROSENFIELD AND A FEW OTHERS IN THE AUDIENCE, CHRIS WHITE, WHO ARE ACTIVE PARTICIPANTS IN THE TRIAL, BECAUSE THEY ACTUALLY HAVE THE EXPERIENCE OF ENROLLING PATIENTS IN THE TRIAL. BUT I'LL TRY TO GIVE YOU SOME GENERAL COMMENTS ABOUT WHY IT'S DIFFICULT TO ENROLL IN RANDOMIZED TRIALS, THIS ONE IN SPECIFIC, AND THEN ALSO TRY TO ADDRESS WHAT CMS MIGHT BE ABLE TO DO.

I THINK ONE OF THE THINGS THAT I ALLUDED TO THIS MORNING IS YOU HAVE THIS BROAD DIVERGENCE IN THE PRACTITIONERS WHO TAKE CARE OF PATIENTS WITH ISCHEMIC RENAL DISEASE. WE'VE HEARD NOW SOME OF THAT SENSE IN THE DISCUSSION THIS MORNING WHERE FOLKS WITH AN INTERNAL MEDICINE BACKGROUND AND NEPHROLOGY VIEW IT AS THERAPY WITH SOME HEALTHY DEGREE OF SKEPTICISM. AND SO TYPICALLY, THE PATIENTS THAT THEY'RE EVEN SCREENING ARE THE ONES WITH RAPIDLY PROGRESSIVE RENAL DYSFUNCTION, OR UNCONTROLLABLE HYPERTENSION ON SIX DRUGS.

IN CONTRAST, FOR THE BELIEVERS, AND I PUT MYSELF IN THAT CAMP, WE THINK THAT THIS IS AN EFFECTIVE THERAPY THAT NEEDS TO BE PROVEN WITH BENEFITS. OFTENTIMES THERE'S ISSUES, LIKE SHOULD I REALLY PUT THIS PATIENT IN THE TRIAL BECAUSE MAYBE I'LL PREVENT THEM FROM GOING INTO KIDNEY FAILURE FIVE

YEARS FROM NOW, OR I'LL HELP CONTROL THEIR BLOOD PRESSURE TO PREVENT CARDIOVASCULAR EVENTS. SO I THINK ONE OF THE FUNDAMENTAL ISSUES AT MANY OF OUR SITES THAT WE'VE VISITED IS THAT YOU HAVE THIS GREAT DICHOTOMY BETWEEN THE HYPERTENSION AND NEPHROLOGY GUYS WHO WON'T SCREEN, LET ALONE REFER FOR INCLUSION IN A TRIAL, AND THE INTERVENTIONAL GUYS WHO FEEL COMPELLED TO TREAT EVERYTHING. AND OBVIOUSLY EACH SIDE HAS ITS OWN DYNAMICS.

DR. SCHWARTZ: AND ALSO THEY HAVE A FINANCIAL DISINCENTIVE.

DR. COOPER: EXACTLY. AND YOU KNOW, THE FINAL ISSUE IS THAT I DON'T THINK WE IGNORE THE FINANCIAL DISINCENTIVE OF PARTICIPATING IN A TRIAL LIKE THIS. YOU KNOW, IF I ENROLLED ONE OF MY PATIENTS INTO CORAL, CMS PAYS ME NOTHING FOR THE TIME THAT I'VE SPENT IN DISCUSSION WITH THE PATIENT, WHEREAS IF I SHORTCHANGE THE DISCUSSION AND SAY SURE, I CAN FIX YOU, AND I PUT IN A STENT, I GET THIS BILL FOR THE ANGIOGRAPHY, I GET THE BILL FOR THE STENT PROCEDURE, AND THE PATIENT THINKS I'M THE GREATEST DOCTOR. AND SO THERE IS A REAL FINANCIAL INCENTIVE FOR A PERSON LIKE MYSELF TO SKIP THE TRIAL AND GO AHEAD AND TREAT THE PATIENT.

WHAT COULD CMS DO IN SPECIFIC? I WOULD

LOVE TO SEE CMS VIEW THIS AS INSTRUMENTAL TO MAKING GOOD DECISIONS. AND AS SOMEBODY WHISPERED IN MY EAR A FEW MINUTES AGO, IF YOU GAVE US A MILLION DOLLARS, NOT A BIG AMOUNT OF MONEY COMPARED TO HOW MUCH YOU'RE SPENDING ON STENTS, WE COULD GIVE THE SITES AN ADDITIONAL $10,000 PER ENROLLED PATIENT AND MAYBE INCENT ENROLLMENT.

YOU KNOW, IN THIS PROCESS YOU HAVE THREE ARMS OF THE FEDERAL GOVERNMENT, THE FDA, CMS AND THE NIH, ALL APPARENTLY WORKING AT CROSS-PURPOSES FOR AN AREA WHERE OVERT ALIGNMENT WOULD BE BENEFICIAL. SO ANYWAYS, I'LL STOP AT THIS JUNCTURE. AND AGAIN, I WOULD LOVE TO HEAR FROM STEVE TEXTOR OR KEN ROSENFIELD OR CHRIS WHITE ABOUT WHAT INVESTIGATORS WHO ARE PARTICIPATING IN THIS TRIAL THINK WE OUGHT TO DO, OR WHAT THE BARRIERS ARE.

DR. TEXTOR: I GUESS I'LL MAKE A COMMENT ON THAT. I THINK ONE WAY OF LOOKING AT THIS -- LET ME JUST COME BACK TO WHAT MIGHT SEEM REPETITIVE, BUT I THINK YOU COULD ARGUE THAT WE'RE COMING FROM A DIFFERENT BACKGROUND THAN THE INTRODUCTION OF OTHER NEW DEVICES. WE'RE COMING FROM A DISEASE WHERE THE STANDARD OF THERAPY HAS BEEN AS LONG AS (INAUDIBLE), WE (INAUDIBLE), YOU COULD ARGUE THAT THE STANDARD OF CARE IS TO REVASCULARIZE PATIENTS WHICH ARE

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THREATENED BY IMPAIRED CIRCULATION. AND REALLY IT'S INTUITIVE AND IT'S NOT INVASIVE, AND THERE MAY BE A MAJOR HAZARD TO LEAVE IT UNTREATED. AND UP UNTIL PROBABLY 10 YEARS AGO OR 15, IT REALLY WAS UNTREATABLE WITH MEDICAL THERAPY.

SO ONE DIFFERENT WAY OF CASTING THIS QUESTION IS REALLY, WHAT'S THE ROLE OF THE CURRENT MEDICAL THERAPY? WE'VE HAD LOTS OF EVIDENCE AND HEARD LOTS OF DATA CONCERNING STATINS AND OTHER AGENTS AND YOU COULD ARGUE, WE REALLY NEED TO SORT THIS OUT IN A HURRY. IF YOU ASK ME WHAT A RATIONAL STEP MIGHT BE, IT WOULD BE TO TAKE THE APPROACH OF THE CANCER INSTITUTE, THAT THE ONCOLOGY GROUP PRACTICING AROUND THE COUNTRY HAS DONE WITH NEW PROMISING THERAPIES. WE'RE NOT SURE WHAT THE OUTCOMES ARE GOING TO BE, WE'RE NOT QUITE SURE IN THIS DISEASE, BUT THERE CERTAINLY IS AGREEMENT AMONG OURSELVES TO ENROLL ALL PATIENTS WITH THIS DISEASE FOR X PERIOD OF TIME. EVEN IF YOU'RE NOT SURE OF THE OUTCOME, WHICH HAS BEEN CLEAR, YOU TAKE THE NEXT 500 OR THOUSAND INDIVIDUALS WITH SMALL CELL CANCER OF THE LUNG TO GET IN THIS TRIAL, BECAUSE WE NEED TO KNOW.

I THINK WE'RE ALMOST IN THIS POSITION WITH THIS DISEASE, NOT SO MUCH BECAUSE OF STENTS PER SE, BUT BECAUSE OF A SHIFT WHERE WE'RE SORT OF SAYING

INTENSIVE MEDICAL THERAPY WILL PROBABLY DO AS WELL OR MAYBE BETTER, WE'RE NOT SURE WE WILL GAIN MUCH WITH THE ISSUE OF REVASCULARIZING KIDNEYS.

BUT THE STIMULATING AND UNIQUE PROBLEM IS WHY WE'RE HAVING THIS DISCUSSION TODAY. WE TAKE THE TACK, YOU KNOW, IN THE PATIENTS I'M SEEING, BASICALLY WE TELL THEM WE'RE NOT SURE OF THE BEST ROUTE. WE WOULD LIKE TO PREVENT THEM FROM RUNNING INTO TROUBLE AND TREAT THEM THE BEST WE CAN. I'M NOT SURE WHETHER STENTS ARE THE WAY TO GO OR NOT, AND THEY ACCEPT THAT, AND BASICALLY WE HAVE NOT HAD THE DIFFICULTY.

AND I THINK THE OBVIOUS FEELING HERE IN THE ROOM IS THAT IT TAKES TIME, IT'S A LOT OF WORK, THERE'S A LOT OF MONEY INVOLVED.

FRANKLY, I THINK WHAT CMS CAN DO IS REALLY REQUIRE COMPLETING THE ENROLLMENT PHASE OF THIS TRIAL BEFORE WE PAY FOR MORE STENTS.

DR. GARBER: CHAIM.

DR. CHARYTAN: COULD THIS QUESTION NUMBER 4 PERHAPS BE BROKEN DOWN INTO TWO OR THREE PARTS?

ONE IS THAT WE WOULD RECOMMEND, OR BOTH IF WE DO SO, FOR A REGISTRY OF ALL PATIENTS WHO UNDERGO THIS PROCEDURE. WE MAY STILL HAVE TO VOTE ON THIS QUESTIONS AS PHRASED, BUT I SUSPECT THE VOTE MIGHT BE

DIFFERENT THAN WHETHER ALL PATIENTS SHOULD BE COVERED ONLY DURING A TRIAL, BUT A SEPARATE QUESTION WHETHER ALL PATIENTS WHO ARE COVERED SHOULD BE PART OF A REGISTRY. AND PERSONALLY, I DON'T KNOW IF THIS IS IN ORDER, BUT IT IS CERTAINLY A RECOMMENDATION THAT SOME SORT OF GROUP BE SET UP TO DEFINE CRITERIA FOR COVERAGE OF THIS PROCEDURE BASED ON CURRENTLY AVAILABLE KNOWLEDGE AND PENDING NEW DATA.

DR. GARBER: WELL, I THINK EXCEPT FOR THE LAST PART, THAT'S APPROPRIATE FOR THIS GROUP. WE HAVE NOT BEEN ASKED TO DEFINE CONDITIONS FOR COVERAGE, WE HAVE BEEN ASKED TO DEFINE WHETHER YOU NEED TO BE ENROLLED IN A QUALIFIED STUDY, AND WE COULD SAY A LITTLE BIT ABOUT IT.

I DON'T KNOW ABOUT THE REST OF YOU, BUT I'VE SAT IN ON MEETINGS ABOUT HOW CMS CAN DECIDE WHAT'S A QUALIFIED STUDY, AND I HAVE NO IDEA.

DR. SALIVE: LET ME CLARIFY WHAT I SAID EARLIER. I THINK THAT, YOU KNOW, WE HAVE IN THE PAST DEFINED WHAT'S A QUALIFIED STUDY, BUT IN AN NCD SUCH AS THIS WE COULD DEFINE WHAT'S A QUALIFIED STUDY. SO WE'RE ASKING YOU, YOU KNOW, IF YOU TOOK THE WORD QUALIFIED OUT AND ANSWERED YES TO THIS QUESTION, THEN WE CAN DISCUSS WHAT ARE THOSE QUALIFICATIONS. SO I'M NOT SAYING WE NEED TO CHANGE THE QUESTION, I'M JUST

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SAYING THAT AS PART OF THE QUESTION, WHAT WOULD BE A QUALIFIED STUDY IN YOUR MINDS, WHAT WOULD THAT BE. SO IF YOU SAY IT SHOULD BE A REGISTRY WITH THE FOLLOWING CHARACTERISTICS, IT SHOULD BE BASED ON CERTAIN PATIENT CHARACTERISTICS, IT SHOULD BE BASED ON CERTAIN FACILITY CRITERIA, THOSE ARE SOME OF THE THINGS WE'RE SEEKING.

DR. SCHWARTZ: THAT GOES TO THE FUNDAMENTAL QUESTION, BECAUSE WHAT I WAS TRYING TO SAY BEFORE IS, MY CONCERN ABOUT A REGISTRY IS THAT A REGISTRY WOULD UNDERMINE THE ABILITY TO, COMPLETELY UNDERMINE THE ABILITY TO HOLD A RANDOMIZED TRIAL. BECAUSE IF IT'S SO MUCH EASIER, I'M GOING TO GET PAID, THE PATIENT IS GOING TO GET THE SERVICE, AND ALL I HAVE TO DO IS FILL OUT A PAGE OR TWO FORM THAT I'LL HAVE MY FELLOW OR SECRETARY OR PATIENT FILL OUT. SO YOU KNOW, I DON'T KNOW THE ANSWER HERE, BUT WE HAVE TO BE REAL CAREFUL ABOUT HOW WE TAKE THIS THROUGH. AND SO IN A GENERAL SENSE, I GENERALLY SUPPORT THIS, BUT THE DEVIL'S IN THE DETAILS HERE AND I DON'T KNOW IF THIS IS SOMETHING CMS HAS BEEN STRUGGLING WITH OR PLAYING AROUND WITH WITH THE BACKDROP OF PULMONARY TRANSPLANTS, LUNG REDUCTION SURGERY, OXYGEN, AND A COUPLE OF OTHER THINGS THEY HAVE TRIED TO PUSH THE ENVELOPE IN TERMS OF GETTING

IT DONE, BUT THIS ONE WILL STILL BE A TOUGH ONE.
DR. GARBER: MIKE, THERE ARE A COUPLE OTHER PEOPLE WAITING TO TALK. YOU'VE HAD YOUR HAND UP FOR A LONG TIME; DO YOU WANT TO GO FIRST?
MR. LACEY: THAT'S FINE.
DR. GARBER: OKAY. DR. DWORKIN, DO YOU WANT TO MAKE A COMMENT?
DR. DWORKIN: WELL, I REALLY JUST WANTED TO AGREE WITH WHAT WAS JUST SAID ABOUT THE POTENTIAL DOWNSIDE OF A REGISTRY. SO, A REGISTRY WILL BE A COLLECTION OF PATIENTS WHO HAVE ALL HAD THE INTERVENTION. IT WON'T REALLY ADDRESS THE FUNDAMENTAL QUESTION OF WHETHER MEDICAL THERAPY, OR WHAT THE COMPARATOR IS BETWEEN THE MEDICAL APPROACH AND THE INTERVENTION.
AND IT COULD BE A HUGE DISINCENTIVE, I THINK, TO ENROLL THEM IN A RANDOMIZED TRIAL, BECAUSE OBVIOUSLY IF YOU PUT A PATIENT INTO A REGISTRY, IT'S A LOT LESS WORK AND EVERY PATIENT GETS STENTED, SO I DON'T THINK THAT WILL HELP THE CORAL TRIAL, INSISTING THAT PATIENTS BE IN A REGISTRY. NOW THAT MAY BE SOMETHING THAT, YOU KNOW, THE GROUP FEELS IS IMPORTANT TO DO, BUT IT'S NOT GOING TO HELP US AND I'M AFRAID IT COULD SERIOUSLY HURT ENROLLMENT INSTEAD.

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DR. GARBER: ACTUALLY I WANTED TO FOLLOW UP ON THAT WITH BOTH YOU AND DR. COOPER, BECAUSE DR. COOPER, I WAS KIND OF SOMEWHAT UNDERSTANDING BUT SOMEWHAT PERPLEXED BY YOUR ANSWER BEFORE ABOUT THE BARRIERS TO ENROLLMENT. UNDOUBTEDLY IT'S VERY DIFFICULT WHEN THE PROVIDER COMMUNITY IS POLARIZED AND YOU HAVE A SET OF PEOPLE WHO ABSOLUTELY BELIEVE THE INTERVENTION WORKS AND A SET OF PEOPLE WHO DON'T, AND SO THEY DON'T WANT THEIR PATIENTS RANDOMIZED. BUT THAT IS NOT AN UNUSUAL SITUATION. IN FACT, MY IMPRESSION OF THE STUFF THAT WE STUDY IN VARIOUS CONTEXTS, THAT'S THE RULE, NOT THE EXCEPTION. USUALLY PEOPLE WHO ARE PASSIONATE ABOUT STUDYING SOMETHING BELIEVE IN IT. I MEAN, THEY MAY BELIEVE IN THE INTERVENTION, THEY MAY BELIEVE IN THE ALTERNATIVE, ONE OR THE OTHER. AND AS SOMEBODY WAS SAYING, THE INTERSECTION OF THOSE MAY BE CLOSE TO EMPATHY.

BUT WHEN YOU LOOK AT SOMETHING LIKE AUTOLOGOUS MARROW TRANSPLANTATIONS FOR BREAST CANCER, IN THAT CASE I WOULD SAY THE OBSERVATIONAL DATA WAS INFINITELY MORE COMPELLING ABOUT THE EFFICACY OF THE PROCEDURE THAN WHAT WE'VE SEEN TODAY. THAT IS TO SAY, THERE WERE HUGE MORTALITY BENEFITS IN THE OBSERVATIONAL STUDIES OF AUTOLOGOUS MARROW

TRANSPLANTATION PATIENTS. AND AS YOU KNOW, THE RANDOMIZED TRIALS, WHEN THEY WERE EVENTUALLY COMPLETED, SHOWED NO BENEFIT OVER CONVENTIONAL CHEMOTHERAPY.

BUT THE ONE THING THAT CAUSED A HUGE SLOWDOWN IN RECRUITMENT IN RANDOMIZED TRIALS WAS WHEN PAYERS STARTED PAYING FOR THE TRANSPLANTATION. IT WAS A HUGE EFFECT AND PROBABLY, I WOULD GUESS, THERE ARE OTHER PEOPLE WHO KNOW A LOT ABOUT THIS, BUT I WOULD GUESS THAT WAS THE SINGLE MOST IMPORTANT FACTOR BEYOND EVERYTHING ELSE.

SO I'M A LITTLE PERPLEXED TO HEAR YOU SAY WELL, IF CMS WOULD JUST GIVE US A MILLION MORE DOLLARS. I DON'T KNOW THAT MUCH ABOUT RENAL ARTERY STENOSIS AND ITS TREATMENTS, BUT BASED ON THE HISTORY OF OTHER INTERVENTIONS, THE FIRST THING A PAYER COULD DO IS SAY WE WILL ONLY PAY IF YOU ENROLL IN A TRIAL, AND THAT WOULD PRESUMABLY HAVE AN IMMEDIATE AND HUGE EFFECT ON ENROLLMENT.

NOW I'M NOT PROPOSING THAT THAT BE DONE, BUT I THINK IT'S IMPORTANT FOR US TO HAVE A CLEAR IDEA ABOUT HOW ALL THE TOOLS THAT CMS HAS AVAILABLE MIGHT WORK. DR. ROSENFIELD, DID YOU WANT TO SAY SOMETHING ON THAT POINT?

DR. ROSENFIELD: JUST A COUPLE OF THINGS

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TO ANSWER THE QUESTION ABOUT ENROLLMENT, BUT ACTUALLY I WAS INTERESTED IN STEVE TEXTOR'S COMMENT BECAUSE WHAT HE'S SAYING IS MEDICAL THERAPY IS THE THING THAT'S CHANGED, SO MAYBE WE SHOULD ACTUALLY START FROM AN INTERVENTION AT THE BASELINE AND ADD MEDICAL THERAPY AS THE EXPERIMENTAL VARIABLE. JUST KIDDING. BUT HONESTLY, I THINK IT'S IMPORTANT TO UNDERSTAND THAT THIS IS DIFFERENT THAN MANY OF THE OTHER THERAPIES THAT HAVE BEEN PRESENTED AS NEW AND NOVEL TREATMENTS. WE'RE TALKING ABOUT RESCINDING SOMETHING THAT HAS BEEN OUT THERE AND MANY, MANY PEOPLE BELIEVE IN ALREADY, AND THAT MAY BE PART OF THE ISSUE -- THAT IS THE ISSUE WITH ENROLLMENT IN THIS TRIAL. IT'S NOT JUST THAT THE INTERVENTIONIST BELIEVES IN THIS, BECAUSE QUITE HONESTLY, I FEEL THAT WE NEED TO GET THE ANSWERS TO THIS QUESTION AS WELL. BUT AS AN INTERVENTIONALIST AT THE END OF THE REFERRAL LINE, I HAVE A SERIES OF GENERAL INTERNISTS, CARDIOLOGISTS AND OTHERS, NONINVASIVE FOLKS WHO REFER IN TO ME, AND PATIENTS THAT EXPECT THAT AT THE END OF THE LINE THEY'RE GOING TO GET REVASCULARIZED BECAUSE THEY'VE BEEN TOLD THAT. SO THERE IS A WHOLE HUGE EDUCATIONAL PROCESS THAT REQUIRES SORT OF UNDOING 15 YEARS OF WHAT WE, MANY OF US BELIEVE WE'VE LEARNED IS AN EFFECTIVE THERAPY.

AND I THINK YOUR POINT IS A GOOD ONE, THAT THIS IS KIND OF A LITTLE BIT, NOT UNPRECEDENTED PERHAPS, I'M NOT SURE OF THE HISTORY WITH CMS AND WHAT THEY'VE DONE IN TERMS OF WITHDRAWING AND RESCINDING COVERAGE, BUT IT CERTAINLY IS GOING TOWARDS THAT DIRECTION AND THAT'S WHY ALL THE DISCUSSION ABOUT MEDICAL ETHICS.

SO, I WOULD ALSO MAKE A COUPLE OF OTHER POINTS. ONE IS THAT THERE HAS BEEN A LOT OF DISCUSSION ABOUT THE NUMBERS RAMPING WAY UP. IF YOU LOOK AT THE NUMBERS OVER THE LAST THREE YEARS, THERE'S ACTUALLY BEEN A SIGNIFICANT PLATEAU EFFECT. IN FACT, OVER THE PAST THREE YEARS, THERE HAS NOT BEEN A SIGNIFICANT CHANGE, SUBSTANTIVE CHANGE IN THE PERCENTAGE OF PATIENTS, THE NUMBER OF PATIENTS UNDERGOING RENAL STENTING. SO, I THINK THAT WAS AN EFFECT OF HAVING A NEW TREATMENT THAT BECAME AVAILABLE IN THE MID '90S, LATE '90S, THAT WAS A MUCH LESS INVASIVE TREATMENT COMPARED TO WHAT WAS AVAILABLE, AND SUDDENLY, YOU KNOW, HAVING IT AVAILABLE, PEOPLE TAKING ADVANTAGE OF IT AND THEN RAMPING UP.

I JUST WANT TO SAY ONE OTHER COMMENT, OR TWO OTHER COMMENTS. ONE WAS, THE COMMENT THAT TIM MURPHY MADE ABOUT WHAT MIGHT BE THE SPECIFIC

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INDICATIONS WERE ACTUALLY THE SAME AS THE AHA/ACC GUIDELINES THAT WERE DESCRIBED EARLIER BY DR. HIRSCH, AND I THINK THAT'S -- WE HAVE -- IT'S INTERESTING THAT DR. MURPHY SAID THE SAME CRITERIA THAT WERE ESSENTIALLY DEFINED BY THESE EXPERTS IN AHA/ACC.

DR. SCHWARTZ: BUT MY GUESS IS THAT 80 PERCENT OF THE PEOPLE GETTING THE PROCEDURE DON'T MEET THAT CRITERIA.

DR. ROSENFIELD: I'M NOT SURE ABOUT THAT, BUT I THINK THAT NONE OF US THAT STOOD UP HERE ON THE INTERVENTIONAL SIDE OR PROMOTING THIS TECHNIQUE SUGGESTED THAT PEOPLE SHOULD BE TREATED PROPHYLACTICALLY. NONE OF US BELIEVES THAT, AND NO DOUBT THERE ARE PEOPLE WHO ARE BEING TREATED PROPHYLACTICALLY AND THEY SHOULD NOT BE TREATED. AND SO IF WE CLEANED UP THAT LITTLE MESS, THAT MIGHT ACTUALLY BE A SIGNIFICANT IMPROVEMENT. BUT I DON'T THINK IT'S 80 PERCENT, AND FOR ANYBODY TO SUGGEST THAT, THERE ARE VERY GOOD -- I WOULD SAY THAT 85 PERCENT OF THE GOOD CLINICIANS OUT THERE ARE MAKING VERY GOOD JUDGMENTS AND IT'S THE 10 OR 15 PERCENT --

DR. SCHWARTZ: I WITHDRAW 80 PERCENT. I WAS JUST MAKING THE POINT THAT IT'S LIKE ANYTHING ELSE, YOU KNOW.

DR. ROSENFIELD: YEAH. AND THE LAST THING

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IS ABOUT REGISTRIES. I THINK REGISTRIES ARE A VERY GOOD THING AND YOU CAN GET A LOT OF INFORMATION FROM THEM. IN THE PCI WORLD AS AN NCDR PERSON, YOU KNOW, THEY ARE ENHANCING OUR KNOWLEDGE BASE GREATLY. I DON'T THINK ACTUALLY -- YOU KNOW, COMPARED TO WHERE WE ARE NOW, I DISAGREE WITH DR. DWORKIN THAT IT WOULD ACTUALLY COMPROMISE OUR ENROLLMENT IN CORAL. I THINK IT WOULD ENHANCE IT, PARTICULARLY COMPARED TO WHERE WE ARE NOW.

NOW IF YOU SAID THE ALTERNATIVE IS TO SAY WE'LL WITHDRAW COVERAGE COMPLETELY UNLESS YOU ENROLL IN CORAL, THEN SURE, THAT'S GOING TO BE THE BEST FOR ENHANCING ENROLLMENT. I DON'T THINK THAT'S A REALISTIC OR PRACTICAL, OR PERHAPS NOT ETHICAL STANCE. HOWEVER, TO SAY LET'S PUT ONE MORE BARRIER, YOU HAVE TO PARTICIPATE IN A REGISTRY, AND THERE ARE MANY OF US IN THE ROOM HERE FROM SVS, ACR AND ACC WHO COULD HELP CONSTRUCT SUCH REGISTRY. THERE ARE SOME ISSUES HERE. YOU WOULD HAVE TO FIGURE OUT WHO IS GOING TO PAY FOR IT. BUT IF YOU SAY YOU CANNOT GET REIMBURSED FOR RENAL STENTING UNLESS YOU PARTICIPATE IN A REGISTRY THAT IS CERTIFIED BY CMS, AND WE'VE GONE THIS ROUTE, DR. SALIVE, WITH OTHER REGISTRIES, IT IS A BARRIER THAT MIGHT ACTUALLY HELP ENROLLMENT IN CORAL. SO I KIND OF DISAGREE ON THAT POINT.

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DR. GARBER: BILL MAISEL, THEN MIKE.
DR. MAISEL: I JUST WANTED TO MAKE THE OBSERVATION THAT A LOT OF THE DISCUSSION HAS FOCUSED ON GETTING THIS RANDOMIZED TRIAL COMPLETED. COMPLETED THIS TRIAL MAY BE FANTASTIC, BUT WE MAY NOT GET ALL THE ANSWERS WE THINK WE'RE GOING TO GET FROM THE RANDOMIZED TRIAL. SO I THINK TO PUT ALL OUR EGGS IN ONE BASKET AND HOPE THAT IN 2009 OR 2010 WE'LL HAVE A DEFINITIVE ANSWER, I THINK IS A LITTLE BIT RISKY, AND I THINK WE HAVE SEVERAL YEARS OF DATA COLLECTION THAT WE COULD GET IN THE MEANTIME.
I AM A PROPONENT OF THE REGISTRY. I THINK THE COMPONENT FACTORS FOR ME WOULD BE THAT IT CANNOT IMPAIR PATIENT ACCESS TO NEEDED PROCEDURES. I THINK WE'VE HEARD FROM A LOT OF THE WELL RESPECTED CLINICIANS AND THE AHA AND ALL THE OTHER PROFESSIONAL SOCIETIES THAT THERE ARE MANY PHYSICIANS WHO ARE WELL RESPECTED WHO STRONGLY BELIEVE THAT THIS IS AN INDICATED PROCEDURE FOR CERTAIN PATIENTS, AT LEAST CERTAIN SUBSETS OF PATIENTS, AND I THINK WE NEED TO BE VERY CAREFUL ABOUT LIMITING ACCESS TO THAT GROUP OF PATIENTS. FOR ME IT WOULD BE THE BILATERAL RENAL ARTERY STENOSIS OR RECURRING PULMONARY EDEMA PATIENT OR WHAT HAVE YOU, I THINK WE COULD CARVE OUT CERTAIN GROUPS.

BUT IF A REGISTRY WAS UBIQUITOUS LIKE AN NCDR REGISTRY, THAT PATIENTS HAD ADEQUATE ACCESS, WE DIDN'T HAVE TO WORRY ABOUT ACCESS TO THE PROCEDURE, THEN I WOULD BE COMFORTABLE WITH THAT.

THE FINAL POINT I WOULD LIKE TO MAKE IS THAT THERE IS PRECEDENT FOR HAVING A REGISTRY TO A PROCEDURE THAT'S ALREADY OUT THERE. IF YOU LOOK AT IMPLANTABLE DEFIBRILLATORS. PRIMARY INTERVENTION OF IMPLANTABLE DEFIBRILLATORS WERE IMPLANTED IN MORE PATIENTS THAN THIS PROCEDURE HAS BEEN DONE IN, AND A REGISTRY WAS REQUIRED THERE, WHICH WAS PAINFUL, BUT IT WAS DONE.

DR. GARBER: MIKE.

MR. LACEY: I JUST WANT TO COMMENT ON THE PERCENT IN SLOWDOWN OR TOTAL NUMBER PERCENTAGE INCREASE. THAT SEEMS TO BE, BOTH FROM COMMENTS THAT WERE WRITTEN BY (INAUDIBLE) AND ALSO BOSTON SCIENTIFIC TODAY THAT SUGGESTED THAT THE INCREASE IS TOPPING OFF. AND IN SOME OF MY CONVERSATIONS, IT SEEMED AS IF PART OF THAT IS THAT AT A LOCAL COVERAGE POLICY LEVEL, MANY OF THE GUIDELINES ARE (INAUDIBLE) AND THE SO-CALLED DRIVE-BY ANGIOGRAPHY IS BECOMING LESS OF AN ISSUE. I'M VERY CONCERNED THAT WHEN YOU START RESTRICTING ACCESS TO 50 OR 60,000 PEOPLE FROM THIS PROCEDURE WITH A VERY CRUDE MEASUREMENT, IT

SHOULD BE MANAGED BY SUGGESTING COMPLIANCE WITH GUIDELINES OR SOME OTHER MORE SUBTLE INCENTIVES THAT DON'T STOP ACCESS TO THIS TECHNOLOGY, BUT RATHER ENCOURAGE BETTER DATA COLLECTION.

DR. GARBER: LINDA.

DR. BERGTHOLD: I WANT TO MAKE A STRONG AND RINGING ENDORSEMENT FOR WHAT CMS HAS BEEN TRYING TO DO, AND I HAVE BEEN ON THE PANEL SINCE THE BEGINNING. THE WHOLE IDEA OF THIS ENTITY WAS TO TRY TO KEEP PATIENTS SAFE AND BE SURE THAT WE DID THE BEST WE COULD TO ASSURE PEOPLE THAT WE WERE PROVIDING TREATMENT FOR WHICH THERE WAS SOME GOOD EVIDENCE OF EFFECTIVENESS. SO THE PRECEDENT THAT I'M HAPPY TO SET IS THE PRECEDENT WHERE WE DO NOT SUPPORT TREATMENTS FOR WHICH THE EVIDENCE IS NOT GOOD FOR EFFECTIVENESS. AND IT DOESN'T BOTHER ME AS A POTENTIAL PATIENT OR CONSUMER AT ALL THAT WE WOULD DO THAT, AND I WOULD HOPE THAT WE WOULD SAVE FOLKS FROM HAVING TREATMENTS THAT WERE OF NOT PROVEN EFFECTIVENESS.

SO I WOULD LEAVE IT UP TO CMS ON THIS QUESTION NUMBER 4 TO DEFINE QUALIFIED CLINICAL RESEARCH STUDIES, BUT I DO REALLY STRONGLY BELIEVE THAT UNTIL WE HAVE BETTER -- I MEAN, I'M HEARING ALL OF YOU ALL SORT OF ARGUING ABOUT WHAT IS EFFECTIVE

AND NOT, AND AS A CONSUMER I'M SAYING, YOU KNOW, IF I NEED THIS, I WANT TO BE SURE THAT THE DATA IS BETTER THAN IT IS TODAY. SO HOWEVER WE GET PATIENTS INTO STUDIES AND WHAT KIND OF STUDIES THEY ARE, I HOPE WE DO GET THEM INTO THOSE STUDIES SO THAT WE CAN MAKE THE DECISIONS BETTER.

DR. GARBER: GO AHEAD, ALAN.

DR. HIRSCH: JUST A QUICK COMMENT TO REITERATE SOME OF THE STATEMENTS I'VE HEARD SAID. YOU KNOW, THE GUIDELINE WRITING COMMITTEE HAD EXACTLY THE SAME CHALLENGE YOU ALL FACE, AND I PITY YOU LIKE I PITIED US. WE SPENT YEARS LOOKING AT THE EVIDENCE, REALIZED IT WASN'T EXCELLENT, WE HAD A SUBTLETY TO MANAGE, WHICH IS TO MEASURE INDIVIDUAL PATIENTS THAT DIDN'T HAVE ACCESS, INDIVIDUAL CONSUMERS, INDIVIDUAL MEDICARE RECIPIENTS IN AREAS WHERE THERE WAS CLASS I AND CLASS IIA, OCCASIONALLY CLASS IIB AREAS WHERE WE THOUGHT THERE REALLY WAS EFFICACY.

NOW (INAUDIBLE) ENTHUSIASM FOR DRIVE-BY ANGIOGRAPHY OR ANGIOPLASTY, PERHAPS THAT WAS BECAUSE THE VASCULAR PROFESSIONAL SOCIETIES DID GET TOGETHER, REVIEW THE EVIDENCE, AND HAVE BEEN UTTERLY UNIFIED IN USING CLINICAL CARE GUIDELINES WITH A LOT OF UNDUE ENTHUSIASM. THAT'S A GOOD PROCESS. SO IT'S NOT ENOUGH TO BE AWARE OF IT. CMS HAS TO ALIGN ITS

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PRIORITIES AND ITS SORT OF POLICY WITH CLINICAL CARE STANDARDS THAT PROFESSIONAL SOCIETIES HELPED CO-CREATE. IF WE DIVERGE THERE, I THINK THERE IS A DANGEROUS PRECEDENT THAT MIGHT BE SET.

SO FROM THE AMERICAN HEART ASSOCIATION VIEWPOINT, WE HAVE TO GO DOWN TO INDIVIDUAL CONSUMER ENTITIES AND CONVINCE THEM OF THE NEED FOR MORE RESEARCH. I ALMOST ALWAYS AGREE WITH STEVE TEXTOR, WE OFTEN END UP AT THE SAME POINT. BUT I AM CONCERNED, STEVE, THAT RESTRICTING ACCESS TO THESE PROCEDURES MERELY TO CLINICAL TRIALS REALLY WILL SET A CHALLENGING PRECEDENT. SO I SIMPLY MAKE THAT STATEMENT AND AGAIN, FROM A POLICY PERSPECTIVE, THAT'S NOT SOMETHING THAT WE SUPPORT.

AND THE THIRD ONE IS, THIS IS A VERY LARGE ONE TO THREE MILLION POPULATION, SO TAKING ONE OF DR. COOPER'S POINTS, IT'S ONE THING TO HAVE A REGISTRY TO LOOK AT ONE OUTCOME OF STENTING, BUT WE DON'T KNOW SOME FUNDAMENTAL THINGS. SO THE NEED FOR BOTH REGISTRIES AND FOR CLINICAL TRIALS IS SUCH THAT WE NEED TO KNOW THE POINT ESTIMATES, THE SAMPLE SIZE REQUIRED, THE RELATIVE RISK REDUCTION IN THE TOTAL POPULATION THAT WE CAN ONLY GET THROUGH A CLINICAL TRIAL. THE RELATIVE BENEFITS AND RISKS BETWEEN THE TWO GROUPS, THE REGISTRY CAN'T GIVE THAT, AND THE

TARGETS WILL CONTINUE TO MOVE.
SO THE PRECEDENT WE SET WITH CMS IS AN ONGOING ONE. I URGE GREAT CAUTION IN YOUR POLICY DECISION.
DR. GARBER: OKAY. LET ME JUST REMIND YOU, PUBLIC SPEAKERS ACTUALLY ARE ONLY RECOGNIZED TO ANSWER QUESTIONS BY THE PANEL, AND WE REALLY WANT TO HEAR FACTUAL ANSWERS. SO I APPRECIATE WHAT YOU SAID, BUT YOU HAD YOUR CHANCE TO SAY YOUR PIECE ABOUT ADVOCATING, AND RIGHT NOW WE REALLY WANT TO JUST GET ANSWERS SPECIFIC TO THE QUESTIONS THE PANEL IS FACING. BILL.
DR. MAISEL: IF WE REALLY WANT TO GET CREATIVE, WE COULD MAKE THE REGISTRY NOT JUST FOR THESE INTERVENTIONS BUT FOR ANYONE UNDERGOING RENAL ANGIOGRAPHY, AND THEN YOU'D HAVE A NICE CONTROL GROUP BUILT IN.
DR. GARBER: I'M GLAD YOU MADE THAT STATEMENT, BECAUSE I HAD A QUESTION FOR THE PANELISTS IN SUPPORT OF A REGISTRY. WHEN I HEARD ABOUT THE REASONS CORAL IS BEING DONE AND THE KINDS OF ENDPOINTS THAT PEOPLE LOOK AT, I WAS WONDERING WHAT YOU WOULD POSSIBLY LEARN ABOUT, FOR EXAMPLE, PROGRESSION TO RENAL FAILURE, FROM A REGISTRY THAT HAD NO CONTROLS. OR WHAT WOULD YOU LEARN ABOUT

CHANGE IN CARDIOVASCULAR RISK. SO I THINK THAT'S A VERY IMPORTANT POINT THAT YOU MADE, BILL, AND I THINK IT'S SOMETHING THAT WE NEED TO FIGURE OUT, WHETHER A REGISTRY IS ACTUALLY GOING TO PROVIDE US WITH GOOD INFORMATION.

IN THE CASE OF THE ICD REGISTRY, THE STRONGEST ARGUMENT MADE IN ITS FAVOR WAS THAT WE DON'T KNOW COMPLICATION RATES IN THE COMMUNITY. BUT THE IDEA THAT YOU COULD ANSWER A QUESTION LIKE WHETHER SOMEONE WITH AN EJECTION FRACTION OF 33 PERCENT BENEFITS FROM ICD, THAT COULD BE ANSWERED BY A REGISTRY, AND NO ONE ARGUED THAT IT WOULD BE HELPFUL. SO THAT KIND OF QUESTION, I THINK THAT SOME OF THE QUESTIONS THAT HAVE BEEN RAISED BY THE PRESENTERS TODAY, IT'S HARD TO IMAGINE ANSWERING IN THE CONTEXT OF A REGISTRY WITHOUT SOME SORT OF CLINICAL TRIAL. BILL.

DR. MAISEL: I THINK THERE ARE SOME IMPORTANT QUESTIONS WHICH COULD BE ANSWERED WITH A REGISTRY, A "SINGLE ARM," PATIENT DOES THEIR OWN CONTROL. CERTAINLY WE'D GET AN IDEA WITH A LARGE NUMBER OF PATIENTS WHAT THE RISK OF ENDING UP WITH END-STAGE RENAL DISEASE OR THEIR CREATININES, WE WOULD BE ABLE TO GET SOME INFORMATION REGARDING RENAL FUNCTION. WITH PHARMACY RECORDS WE MIGHT GLEAN SOME

INFORMATION ABOUT TREATMENT, I'M NOT SAYING THAT IS GOING TO BE HIGH QUALITY DATA, BUT IT WILL BE MORE THAN WE HAVE.

I THINK IT WOULD BE AMAZING IF WE COULD GET RENAL ANGIOGRAPHY REGISTRY DATA, BUT I DON'T KNOW THE NUMBERS OF PATIENTS THAT ARE UNDERGOING RENAL ANGIOGRAPH, AND I DON'T KNOW THAT I WOULD USE THE WORD ETHICAL, BUT I DON'T KNOW IF IT MAKES MONETARY SENSE TO ENROLL ALL THOSE PATIENTS IN A REGISTRY TO LOOK AT THEM.

DR. GARBER: WELL, YOU COULD CHANGE THE RECOMMENDATION TO SAY THAT CMS DEVELOPS AN APPROPRIATE CONTROL GROUP FOR REGISTRY, WHETHER IT'S BASED ON RENAL ANGIOGRAPHY OR SOME OTHER KIND OF INDICATOR. CAROLE.

DR. FLAMM: JUST TO EXTEND ON THAT IDEA, THE NOTION OF PUTTING THIS INTO A CLINICALLY DEFINED POPULATION, PERHAPS THOSE WITH RENAL ARTERY STENOSIS, THOSE THAT MEET THIS CLINICAL POPULATION OF INTEREST, AND FIND SOME WAY TO PROVIDE SOME SORT OF LONGITUDINAL GATHERING OF INFORMATION TO LEARN MORE THAN WE KNOW TODAY. I DON'T KNOW THAT IT WILL BE THAT EFFECTIVE.

DR. GARBER: OR TO MODIFY THE QUESTION TO SOMETHING THAT'S MORE AMENABLE.

DR. CHARYTAN: COULD WE MODIFY IT INTO THE TWO CATEGORIES, THE FIRST ONE BEING VOTING FOR THE REGISTRY AND THE SECOND ONE BEING WHETHER PATIENTS SHOULD BE COVERED ONLY AS FAR AS THE TRIAL? I FEEL MUCH MORE COMFORTABLE VOTING ON THOSE TWO SEPARATELY.
DR. GARBER: WHAT'S THE SENSE OF THE PANEL? THERE'S A SPECIFIC THING THAT BARRY SAID BEFORE, AND I WANT TO MAKE SURE THAT YOUR PROPOSAL IS THE SAME. BARRY SAID THAT FOR THE INDICATIONS FOR WHICH IT IS COVERED, EVERY MEDICARE ENROLLEE MUST BE ENROLLED IN A REGISTRY TO BE ELIGIBLE FOR REIMBURSEMENT. IS THAT WHAT YOUR PART A IS?
DR. CHARYTAN: WELL, THAT'S A DETAIL. I CERTAINLY WOULD HAVE NO PROBLEM WITH THAT. BUT IF WE DEFINE OR WE RECOMMEND THAT A REGISTRY BE SET UP, SOMEONE WOULD OBVIOUSLY HAVE TO SET UP AND DEVELOP THE DETAILS THAT GO INTO THAT IF WE WANT TO DO THAT. I WOULD HAVE NO PROBLEM WITH WHAT YOU JUST SAID, BUT I THINK A REGISTRY OUGHT TO BE SET UP AND I WOULD CERTAINLY BE IN FAVOR OF THAT.
DR. GARBER: SO THE QUESTION ON THE TABLE NOW IS WHETHER THIS SHOULD BE THE VOTING QUESTION. MARK?
DR. FENDRICK: KNOWING THAT YOU WILL TAKE A STRAW POLL EVENTUALLY, I WOULD KEEP IT THE WAY IT

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IS. I THINK FOR SOMEONE WHO HAS BEEN AROUND A GOOD BIT OF TIME, THE FACT THAT WE ACTUALLY HAVE AN EXPLOSIVE QUESTION ABOUT PROVISIONAL COVERAGE WITH EVIDENCE DEVELOPMENT IS A HUGE STEP FORWARD. JUST THAT QUESTION, WHETHER WE BELIEVE IT'S -- GOING TO DR. COOPER'S POINT -- NOT ONLY DO QUALIFIED CLINICAL RESEARCH STUDIES, WHILE THEY DIFFER BY RIGOR, THEY ALSO DIFFER SUBSTANTIALLY BY HOW MUCH THEY COST, AND I THINK WE WOULD DECIDE HOW MUCH, WHICH TRIALS TO DO IF WE KNEW HOW MUCH MONEY WE HAD, WHICH WE CLEARLY DON'T. SO I WOULD ARGUE TO KEEP THE QUESTION THE WAY IT IS.

DR. CHARYTAN: BUT MY, AGAIN, MY STRONG CONCERN IS THAT IF WE LEAVE IT AS IS, SOMEONE MAY INTERPRET THIS AS SUPPORT FOR COVERAGE ONLY AS PART OF THE STUDY AND I THINK THAT, AGAIN, IS SETTING A VERY, VERY DANGEROUS PRECEDENT. AND I APPRECIATE WHAT YOU SAID, THAT A REGISTRY IS INCLUDED AS A STUDY, BUT I FELT AND I SUSPECT MANY OF US HAVE FELT WITH CMS IS THAT WHAT WE INTEND TO RECOMMEND IS NOT ALWAYS THE WAY THINGS ARE IMPLEMENTED. AND THAT'S WHY WE MUST BE VERY CLEAR THAT WE SUPPORT A REGISTRY, BUT NOT NECESSARILY RESTRICTING COVERAGE TO ONLY THOSE PATIENTS WHO ARE PART OF A STUDY.

DR. GARBER: SANDY.

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DR. SCHWARTZ: I THINK THE UNEASE HERE IS TWOFOLD. ONE IS ON THE ONE HAND, I'M A LITTLE LOATH TO SPECIFY SPECIFIC RESEARCH DESIGN TO CMS AT THIS POINT. BUT I THINK THAT THERE IS A DIFFERENCE BETWEEN SOMETHING THAT HAS BEEN OUT THERE AND USED IN THE ABSENCE OF WHAT I WOULD CONSIDER GOOD EVIDENCE ON IT, THERE'S STRONG ACCESS TO IT WITH CLEAR INDICATIONS, AS OPPOSED TO SOMETHING WHICH IS DE NOVO AND JUST COMING ON THE MARKET.

SO I AGREE WITH MARK, I WOULD SORT OF LIKE TO KEEP IT THE WAY IT IS WITH THE SENSE OF THE GROUP BEING, OR THE COMMENTS BEING MAYBE SOMETHING SPECIFIC THAT THIS DOESN'T, THAT THIS SHOULDN'T BE IMPLEMENTED IF IT MEANS WITHDRAWING ACCESS FOR PEOPLE WHO MEET CLEARCUT INDICATIONS AS PER THE PROFESSIONAL SIDE, WHICH I THOUGHT DID A VERY GOOD JOB. AND I WAS SURPRISED, HAVING DONE GUIDELINES FOR 30 YEARS, WITH THE LEVEL OF CONSENSUS.

DR. GARBER: YEAH, THE LEVEL OF CONSENSUS GIVEN THE LEVEL OF EVIDENCE. BILL.

DR. LEWIS: I THINK THERE ARE TWO ISSUES HERE. ONE IS, I DON'T THINK WE SHOULD REALLY WORRY TOO MUCH ABOUT WITHDRAWING SUPPORT FOR UNINDICATED PROCEDURES. SO THAT IF YOU MEET CLASS I OR CLASS IIB INDICATIONS, AS THE AHA'S ARGUED, YOU KNOW, MAYBE

THOSE PEOPLE GO ON REGISTRIES, AND THE OTHER ONES, I DON'T THINK THAT THEY SHOULD -- I MEAN, WE'RE TALKING ABOUT DRIVE-BY SHOOTINGS AGAIN, AND THAT'S PROBABLY NOT THE GREATEST THING IN THE WORLD, SO I DON'T HAVE ANY PROBLEM WITH TRYING THAT.

THE SECOND POINT TO MAKE ABOUT THIS IS AS ONE WHO FILLS OUT A SHEET EVERY TIME HE PUTS IN AN IMPLANTABLE DEFIBRILLATOR, I DON'T THINK IT'S TOO MUCH OF A -- IT DOESN'T RESTRICT MY ABILITY TO ACTUALLY ENROLL PATIENTS BY PUTTING THEM IN THAT REGISTRY. I THINK THAT THERE IS SOME LIMITED AMOUNTS OF DATA THAT COULD BE GAINED FROM THAT BASED ON AN IDEA OF WHAT THE ABILITY AND THE NUMBERS OF PROCEDURES ARE FOR A CERTAIN INDIVIDUAL PERFORMING THEM, AND WHATEVER COMPLICATION RATES ARE, I THINK THERE IS VALUABLE INFORMATION WITH A REGISTRY.

DR. GARBER: BARRY.

DR. PRESSMAN: FIRST I WANT TO CLARIFY.

IF WE VOTE ON THE QUESTION AS IT IS, AND MOST IF NOT ALL OF US ARE SAYING, I THINK, THAT WE REALLY DON'T BELIEVE THAT ALL PATIENTS SHOULD BE IN CLINICAL TRIALS INSTEAD OF A REGISTRY, THEN I THINK YOU WOULD FIND THAT WE STRONGLY DISAGREE. THEN WE WOULDN'T HAVE THE PROBLEM. AS WAS SUGGESTED, EITHER YOU COULD HAVE A STRAW POLL ON ADDITIONAL CRITERIA AND/OR A

REGISTRY, SO YOU COULD BREAK IT UP IN TWO, OR WE COULD ADD TWO OTHER QUESTIONS HERE.

I THINK WE'RE CLEAR ON WHAT MOST OF US IS SAYING IS A FIVE, THEN I DON'T THINK WE'RE GETTING TO THE NATURE OF IT IF CMS WILL KEEP IT AS QUALIFIED TRIALS.

DR. GARBER: SO, JUST FOR POINT OF CLARIFICATION HERE, AGAIN, I DON'T KNOW IF THEY'RE USING QUALIFIED WITH A CAPITAL Q, MEANING SUBJECT TO THE HHS POLICY, WHATEVER IT IS. THAT DOES NOT REQUIRE THAT IT BE A RANDOMIZED CLINICAL TRIAL. A REGISTRY COULD QUALIFY. SO IF YOU THINK EVERYBODY SHOULD BE IN A REGISTRY AT A MINIMUM, THEN YOU WOULDN'T VOTE FIVE ON THIS.

(INAUDIBLE COLLOQUY AMONG PANELISTS.)

DR. GARBER: ACCORDING TO AT LEAST THE EXISTING POLICY, FOR EXAMPLE, THERE'S SOMETHING CALLED DEEMING, AND IT INCLUDES PHASE ONE STUDIES OF DRUGS BEING CONDUCTED AT NCI-DESIGNATED CANCER CENTERS. SO THAT IS NOT RANDOMIZED, IT'S NOT EVEN REALLY CONTROLLED, PLUS THE DOSE-RESPONSE STUDIES. SO A REGISTRY ACTUALLY COMES CLOSER TO A CONTROLLED STUDY THAN THAT. SO THE EXISTING CLINICAL TRIALS DEFINITION, AGAIN, I DON'T REALLY KNOW WHAT IT IS AT THIS MOMENT, BUT IT INCLUDES STUFF THAT'S PURELY

OBSERVATIONAL AND STUFF THAT MOST OF US WOULD THINK BARELY QUALIFIES AS A STUDY, PERIOD. SO I THINK, MARCEL, MAYBE YOU WANT TO COMMENT MORE ABOUT THIS.

DR. SALIVE: YES, CMS DEFINITELY INCLUDES REGISTRIES UNDER THIS QUESTION, IF I WAS UNCLEAR BEFORE. MOST OF OUR POLICIES DEALING WITH COVERAGE AND EVIDENCE DEVELOPMENT HAVE ARTICULATED THOSE AS SOME OF THE OPTIONS, A REGISTRY, A PROSPECTIVE STUDY, A RANDOMIZED TRIAL. THERE ARE SOME THINGS NOT INCLUDED, AND I THINK THOSE ARE MORE IN THE REALM OF RETROSPECTIVE STUDIES GOING BACK, BUT IT'S HARD TO ENVISION HOW THAT WOULD BE IMPORTANT, SINCE COVERAGE IS DONE PROSPECTIVELY.

DR. GARBER: SO, ARE WE CLEAR ABOUT THAT? THIS DOESN'T MEAN RANDOMIZED, IT'S A PRETTY BROAD DEFINITION.

DR. TEXTOR: LET ME JUST ASK SOMETHING. HOW DOES CMS, HOW SHOULD ONE APPROACH THE ISSUE OF IDENTIFYING AND DECLINING COVERAGE ON OBSOLETE PROCEDURES?

DR. SALIVE: THAT'S A GOOD QUESTION. I THINK IN GENERAL WE HAVE NOT GONE BACK TO OBSOLETE PROCEDURES TO NONCOVER THEM, SO YOU KNOW, WE HAVEN'T DEALT WITH THAT VERY MUCH FRANKLY.

DR. GARBER: MIKE.

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MR. LACEY: DOES THIS QUESTION ALSO APPLY TO SURGERY AS WELL?
DR. GARBER: YES.
MR. LACEY: (INAUDIBLE.)
DR. SALIVE: I THINK YOU HAVE TO SPECIFY. THIS CASTS A WIDE NET IN THE QUESTION. WE ARE ASKING THE PANEL TO WEIGH IN BEYOND JUST VOTING ON HOW WOULD YOU DEFINE A STUDY THAT YOU WANT TO SEE. IF THE VOTE IS ON THE AGREEMENT SIDE OF THIS QUESTION, WHAT KIND OF STUDY WOULD YOU WANT TO SEE? SO WE'VE HAD A GOOD DISCUSSION SO FAR, AND IF YOU DON'T WANT TO SEE STUDIES OF SURGERY, PLEASE SAY THAT. IF YOU DO WANT TO SEE THEM, PLEASE SAY THAT.
MR. LACEY: I'M JUST TRYING TO GET A SENSE OF ACCESS TO CARE AND HOW THIS MIGHT IMPACT THAT. AND MY CONCERN IS, AGAIN, THAT BY REQUIRING THAT AS A CONDITION FOR COVERAGE, THAT YOU WOULD LIMIT ACCESS TO CARE FOR PEOPLE, AND IF THERE WERE OTHER WAYS FOR YOU TO ENCOURAGE DATA COLLECTION. AND THEN LASTLY, IT REALLY DOES SEEM, THE FUNDAMENTAL QUESTION HAS TO HAVE A CONTROL OR CONTROLLED STUDY. A REGISTRY COULD ANSWER SOME QUESTIONS THAT ARE RELEVANT, BUT WE CAN ALWAYS ASK FOR MORE DATA TO GET TO THE KEY POINT THAT YOU REALLY WANT, WHICH IS A COMPARISON BETWEEN MEDICAL AND SURGICAL.

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DR. SCHWARTZ: BUT THE WAY I'M THINKING ABOUT IT IS THAT THE PURPOSE FOR REQUIRING THEM TO ENROLL IN A CLINICAL TRIAL IS NOT TO CONTROL ACCESS. THE ACCESS, I THINK, IN THIS SITUATION IS CONTROLLED BY THE INDICATIONS OF APPROPRIATENESS. THE REASON FOR (INAUDIBLE) FAVOR OF A REQUIREMENT TO REQUIRE SOME INVOLVEMENT IN SOME SORT OF CLINICAL STUDY IS TO FACILITATE AND EXPEDITE COLLECTION OF DATA THAT EVERYONE AGREES NEEDS TO BE DONE SO THAT IT DOESN'T TAKE 20 YEARS, WE MIGHT SEE IT IN THREE TO FIVE YEARS. BUT FOR ME IT'S A MATTER OF, YOU KNOW, WITHIN THIS CONTEXT, NOT BEING RESTRICTIVE, BUT THE GOAL BEING TO GENERATE EVIDENCE IN AN EXPEDITIOUS FASHION.
MR. LACEY: THAT'S FAIR, BUT AS SAID BEFORE, WITH A REGISTRY, IT DEPENDS ON WHAT YOU'RE REGISTERING. YOU KNOW, (INAUDIBLE) FOCUSED ON A PROCEDURE, BUT FOCUSED ON A PATIENT POPULATION. YOU COULD TAKE A REGISTRY AND WE COULD CREATE CONTROL GROUPS BUT (INAUDIBLE).
DR. GARBER: BILL.
DR. MAISEL: I AM NOT IN FAVOR OF HAVING SURGICAL PATIENTS IN A REGISTRY. I THINK THE FRAMEWORK FOR INTERVENTIONAL PATIENTS SUCH AS CORONARY OR CAROTID REGISTRIES ARE ALREADY THERE. I DON'T THINK IT'S A HUGE LEAP TO ADD RENAL STENTING

AND BALLOON ANGIOPLASTY TO THAT. I'M ALSO NOT SURE HOW MANY PATIENTS ARE ACTUALLY UNDERGOING THE SURGERY, IF IT'S 20,000 A YEAR GETTING STENTS, YOU KNOW, MAYBE SOMEONE HAS AN IDEA, BUT I DON'T THINK IT'S THAT LARGE. SO I DON'T THINK THAT'S NECESSARY.
DR. CHARYTAN: COULD I ASK A QUESTION? IF THE CONSENSUS SEEMS TO BE THAT WE ALL SUPPORT A REGISTRY, IS THERE ANY REASON WHY THIS QUESTION COULDN'T BE REWORDED IN A POSITIVE WAY, THAT IS, THAT THE PANEL VOTES TO SUPPORT A REGISTRY AND --
DR. GARBER: THAT IS A VERY DIFFERENT QUESTION. I MEAN, YOU CAN REDUCE THE ANSWER, BUT I WOULD SUGGEST THAT YOU CAN, WE CAN HAVE A FOLLOW-ON QUESTION AFTER WE VOTE ON THIS ONE, BUT THAT'S A COMPLETELY DIFFERENT QUESTION FROM THIS.
SO THE POINT IS, FIRST OF ALL, I JUST WANT TO MAKE SURE, ARE PEOPLE COMFORTABLE VOTING ON THE QUESTION AS STATED AT THIS POINT IN THE DISCUSSION? I SEE A LOT OF NODS. SO WHY DON'T WE FIRST VOTE AND THEN EXPLAIN YOUR ANSWER. FOR EXAMPLE, BILL JUST SAID HE WOULD NOT INCLUDE SURGICAL CASES IN A REGISTRY, SO HE WOULD EXEMPT THAT. BUT HE MIGHT SAY BUT I WOULD IN OTHER CASES. SO IN ANY CASE, THE MOST IMPORTANT THING IS TO EXPLAIN HOW YOU VOTED.
OKAY. YOU WANT TO PUT UP THE NUMBERS?

(MEMBERS OF THE PANEL VOTED, RESULTS WHICH WERE RECORDED BY STAFF.
DR. GARBER: THIS MUST BE OUR HIGHEST VARIANCE VOTE OF THE DAY. WHO WANTS TO START EXPLAINING YOUR VOTES?
DR. TEXTOR: I DON'T MIND. MY VIEW IS THAT THIS IS A PRESSING AREA WITH TREMENDOUS AMBIGUITY, WE'VE HEARD ABOUT IT TODAY. I THINK WE REALLY NEED TO DEFINE FOR THE MEDICARE POPULATION THE NET GAINS AND BENEFITS OF MEDICAL THERAPY WHICH WE NOW ALL ACCEPT, ALBEIT INTENSIVE AS DISCUSSED BEFORE, WITH INTERVENTIONAL THERAPIES, ALSO WHICH ARE BEING WIDELY PRACTICED. AND I THINK THE ONLY WAY WE COULD ANSWER THAT IS REALLY TO LIMIT COVERAGE TO THOSE PEOPLE WHO ARE ENROLLED IN TRIALS THAT WILL GIVE US MORE INFORMATION.
DR. EDWARDS: I WOULD LIKE TO ECHO PARTS OF WHAT DR. TEXTOR SAID. I CERTAINLY THINK THAT THIS IS AN ISSUE BASED JUST ON THE SHEER NUMBERS OF INDIVIDUALS AFFECTED AND THE POTENTIAL RAMIFICATIONS FOR THOSE INDIVIDUALS, THAT THIS IS A MATTER OF GREAT PUBLIC HEALTH SIGNIFICANCE. AND ALTHOUGH I TIP MY HAT TO THE INDIVIDUALS WHO SLAVED IN THE ROOMS IN THE HOTELS TO COME UP WITH CONSENSUS GUIDELINES, I PERSONALLY FEEL THE CONSENSUS IN PRACTICE GUIDELINES

SHOULD APPLY TO SITUATIONS TOO RARE TO STUDY OR IN SITUATIONS WHERE WE POSSIBLY HAVE AN OUTDATED INTERVENTION, A NEW INTERVENTION COMING ON, WHERE IT MAY NOT BE ETHICAL OR FEASIBLE OR PRACTICAL TO STUDY IT DIRECTLY.

THIS IS NOT ONE OF THOSE CONDITIONS. TENS OF THOUSANDS OF THESE PROCEDURES ARE DONE EACH YEAR AND WE OUGHT TO BE ABLE TO GET SOME MEANINGFUL INFORMATION RATHER EXPEDITIOUSLY AND ANSWER A LOT OF THE QUESTIONS THAT REMAIN, AND NOT TO DO SO I THINK WOULD BE A PRETTY POOR STATEMENT.

DR. GARBER: ANY OTHER COMMENTS? BILL.

DR. MAISEL: I HAVE THE UNIQUE DISTINCTION OF BEING THE ONLY ONE WHO HELD UP THE NUMBER THREE, AND I VOTED THREE BECAUSE DR. COOPER'S A BIMODAL PERSON. I FELT THAT I WANTED TO VOTE A ONE AND A FIVE. I FELT STRONGLY THAT SOME PATIENTS SHOULD NOT NEED TO HAVE DATA COLLECTED ON THEM, I THINK THE CONSENSUS OF THE CLINICAL COMMUNITY IS THAT THERE ARE CERTAIN PATIENTS WHO NEED THIS PROCEDURE AND I THINK THEY SHOULD HAVE ACCESS TO IT. BUT ON THE OTHER HAND, I THINK THE VAST MAJORITY OF PATIENTS UNDERGOING THIS PROCEDURE SHOULD HAVE THE DATA COLLECTED ON THEM.

DR. GARBER: LET ME JUST ASK FOR THE

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PEOPLE WHO VOTED FIVE, DOES EVERYBODY AGREE THAT THERE IS A SUBSET OF PATIENTS FOR WHOM DATA NEED TO BE COLLECTED, WHETHER IT'S A REGISTRY OR NOT?
MR. LACEY: I DO, I FEEL THAT HAVING COVERAGE CONDITIONED UPON PARTICIPATION WILL INHERENTLY RESTRICT ACCESS.
DR. GARBER: BUT YOU ARE SAYING THAT THERE'S SOME SUBGROUPS FOR WHOM YOU THINK THAT'S APPROPRIATE, OR NOT?
MR. LACEY: YES, IT DOES SEEM THAT.
DR. CHARYTAN: I ABSOLUTELY AGREE. MY CONCERN WAS A DIFFERENT ONE, NOT TO RESTRICT THE PROCEDURE IN SOME PATIENTS WHO ARE NEEDED, AND I POINTED OUT THAT WE OUGHT TO HAVE STRICT CRITERIA. SO MY FIVE WAS PROCEDURAL, IF YOU WILL, AND BASED ON THE EXPERIENCE OF DEALING WITH CMS, AND FORGIVE ME, AND OUTCOMES THAT MAY BE OTHER THAN WHAT'S INTENDED. AND I THINK WE HAVE TO BE CAREFUL IN CONFUSING GOALS AND THE WAY THE BUREAUCRATIC SYSTEM WORKS.
DR. GARBER: SO I WANT TO MAKE SURE THAT WE GET ON THE RECORD HOW THE ENTIRE PANEL FELT. I THINK THERE IS A CONSENSUS AMONGST EVERYONE THAT THERE IS A SUBSET OF PATIENTS FOR WHOM ABSOLUTELY DATA NEEDS TO BE COLLECTED AS A CONDITION OF COVERAGE, WHETHER IT'S REGISTRY OR TRIAL. WE DIDN'T

GET INTO TOO MUCH DETAIL ABOUT WHAT THAT MIGHT BE.
THERE ARE SOME PEOPLE WHO THINK DATA NEEDS
TO BE COLLECTED FOR EVERY PATIENT WHO GETS THE
PROCEDURE, AND I THAT'S THE PEOPLE WHO VOTED ONE ON
THIS QUESTION.
AND DOES THAT ENCOMPASS EVERYONE SOMEWHERE
ALONG THAT SPECTRUM? BARRY?
DR. PRESSMAN: I VOTED TWO, EVEN THOUGH I
RAISED THE IDEA OF A REGISTRY. I FELT LIKE CHAIM
DID, THERE ARE SOME PATIENTS WHO OUGHT TO BE ABLE TO
GET IN EVEN IF YOU CAN'T GET INTO A REGISTRY, BUT
THEY MUST FULFILL CERTAIN CRITERIA, WHATEVER THOSE
CRITERIA ARE. I DON'T THINK IT SHOULD BE THE WILD
WILD WEST, WHERE A DOCTOR JUST CHOOSES ON HIS OWN AND
EXPECTS TO GET REIMBURSED, THERE HAS TO BE SOME
CLINICAL LOGIC TO IT, SO THAT'S WHY I VOTED TWO.
DR. GARBER: OKAY. ANY OTHER COMMENTS?
NOW YOU GET YOUR CHANCE TO HAVE SOME
DISCUSSIONS OF THE STRENGTHS OF THE TRIALS. I DON'T
KNOW HOW MUCH PEOPLE WANT TO DISCUSS THESE PARTICULAR
TRIALS. IT WAS JUST SOMETHING TO SORT OF EXPAND ON
ANY DEFICIENCIES YOU MIGHT THINK OF AND ANY GAPS IN
WHAT KIND OF INFORMATION IS AVAILABLE. BILL.
DR. MAISEL: I WAS JUST CURIOUS, AND MAYBE
ONE OF THE CORAL INVESTIGATORS CAN COMMENT. THIS IS

00272

AN UNBLINDED STUDY, AT LEAST ACCORDING TO THE PROTOCOL THAT I READ. OBVIOUSLY SOMEONE COULD ARGUE IS DOES MATTER IN MORTALITY, WHAT HAVE YOU, BUT CARDIOVASCULAR ENDPOINTS YOU COULD ARGUE COULD BE AFFECTED BY BIAS OR LACK OF BLINDING. WHY AREN'T THE PATIENTS BLINDED?

DR. DWORKIN: I MEAN, IT'S A PRACTICAL ISSUE. HOW CAN YOU BLIND SOMEBODY TO WHETHER THEY'VE HAD A RENAL ARTERY INTERVENTION? IT'S NOT EASY TO DO.

DR. MAISEL: HOW ABOUT PATIENTS UNDERGOING ANGIOGRAPHY?

DR. DWORKIN: NOT ANYMORE. WE HAVE NONINVASIVE PATHWAYS NOW BY ULTRASOUND, BY MR, SO FROM A PRACTICAL POINT OF VIEW IT WOULD REALLY BE IMPOSSIBLE TO BLIND PATIENTS AS TO WHETHER THEY WERE GETTING INTERVENED OR NOT.

THAT BEING SAID, THE MEDICAL INTERVENTION IS EXACTLY THE SAME FOR BOTH ARMS OF THE STUDY, AND WE HAVE SPECIFIC TARGETS FOR BLOOD PRESSURE, CHOLESTEROL, HEMOGLOBIN A1C, ET CETERA, ET CETERA, ET CETERA, AS WELL AS A REPORT CARD SYSTEM AND A COMMITTEE THAT'S MONITORING SITE PERFORMANCE IN TERMS OF MEETING THESE THREE TARGETS. THAT APPLIES TO BOTH ARMS OF THE STUDY. SO THE MEDICAL INTERVENTION IS

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IDENTICAL, THE TARGETS ARE IDENTICAL, AND IF THE PROTOCOL FUNCTIONS AS IT'S DESIGNED, THERE WON'T BE DIFFERENCES IN BLOOD PRESSURE, LDL CHOLESTEROL AND ALL OF THESE OTHER CARDIOVASCULAR RISK FACTORS THAT WE'RE TRYING TO CONTROL BETWEEN THE TWO GROUPS.
WHAT THE STUDY WILL REALLY ANSWER IS WHETHER RENAL ISCHEMIA PER SE, EVEN INDEPENDENT OF SOME OF THESE CONSEQUENCES LIKE HYPERTENSION ACTUALLY DRIVES ADVERSE OUTCOMES. AND THAT COULD OCCUR BECAUSE OF DIFFERENCES IN KIDNEY FUNCTION, DIFFERENCES IN THIS NEUROHUMORAL ACTIVATION AND WHETHER OR NOT YOU CAN REALLY ADEQUATELY INTERRUPT IT OR AS EFFECTIVELY INTERRUPT IT AS YOU CAN BY REVASCULARIZATION.
ONE OF THE REVIEWERS OF THE STUDY SUGGESTED THAT THE ADVANTAGE OF INTERVENING IN RENAL ARTERIES MIGHT BE THAT IT WILL ALLOW MORE PATIENTS TO GET RENAL ANGIOTENSIN BLOCKING, AND THAT MIGHT BE THE WHOLE BENEFIT, WHICH IN TERMS OF THE CLINICAL TRIAL WOULD BE FINE, BECAUSE IT STILL SHOWS A DIFFERENCE BETWEEN THE TWO APPROACHES, ALTHOUGH MAYBE NOT THE ONE THAT PEOPLE ARE ACCEPTING OR EXPECTING.
BUT I THINK WE ARE TRYING TO ADDRESS THIS ISSUE OF BIAS IN TERMS OF THOSE OTHER RISK FACTORS VERY AGGRESSIVELY IN THE TRIAL.

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DR. TEXTOR: ALAN, COULD I COMMENT? I THINK IT'S VERY HELPFUL, AND I APPRECIATE THE EFFORT PEOPLE HAVE GONE THROUGH TO LOOK AT THE TRIALS IN PROGRESS, BECAUSE WE NEED TO KNOW ABOUT WHAT'S OUT THERE. I AM IMPRESSED WITH HOW WEAK THOSE TRIALS ARE. I THINK IF ONE LOOKS AT THEM, MANY OF THEM SORT OF BUY INTO THIS VERY DIFFERENT FRAMEWORK OF WHAT THEY EXPECT THE OUTCOMES TO BE.

STAR, IF YOU LOOK AT IT, ASSUME THAT WITH 120 PATIENTS, THEY'RE ASSUMING THAT 50 PERCENT OF THESE ARE GOING TO PROGRESS TO END-STAGE RENAL DISEASE. ALTHOUGH THEY HAVE EXCLUDED OR STRATIFIED FOR BOTH BILATERAL AND UNILATERAL DISEASE, THEY INCLUDE PEOPLE WITH MALIGNANT HYPERTENSION, AND I THINK IT'S ALMOST CERTAINLY GOING TO BE A NEGATIVE PROBLEM. RENAL ARTERY STENOSIS IS DEFINED BY MRA OR CTA ONLY.

YOU KNOW, WE HAVE A LONG EXPERIENCE THAT IT'S VERY LIKELY THAT THESE TRIALS ARE NOT GOING TO SEE THE RATES OF PROGRESSION THAT THEY EXPECT. WE DON'T THINK IT'S GOING TO HAPPEN AND WE HAVEN'T HEARD OF AN OUTCOME FROM THE STUDIES STARTED AND FINISHED.

THE SAME IS TRUE FOR RAVE. THEY ARGUE THAT THEIR PRIMARY OUTCOME IS LOSS OF KIDNEY FUNCTION, BUT IN THAT TRIAL THEY HAD EXCLUDED PEOPLE

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WITH (INAUDIBLE) VERY ENLIGHTENING FIVE YEARS FROM NOW TO ANSWER THIS QUESTION, AND THAT'S PART OF MY RATIONALE, THAT IF WE ANTICIPATE RAMPING UP PARTICIPATION IN TREATMENT TO 35,000 OR MORE A YEAR, WE REALLY OUGHT TO ANSWER THIS QUESTION WITH STUDIES THAT ARE WELL DESIGNED, DONE IN THE UNITED STATES, THAT WE CAN HANG OUR HATS ON.

DR. GARBER: MARK.

DR. FENDRICK: AND QUICKLY FOR THE RECORD, AS ONE WHO HAS DURING MY TENURE SPENT AN AWFUL LOT OF TIME RANTING AND RAVING ABOUT BIASES THAT ARE ALREADY IMPLEMENTED INTO THE DESIGN OF CLINICAL TRIALS, I WANT TO COMMEND THE CORAL INVESTIGATORS FOR ACTUALLY DOING ALMOST EVERYTHING YOU CAN TO SHOW EXPLICITLY THAT THE INTERVENTION ON THE RENAL ARTERY IS GOING TO BE THE INTERVENTION THAT SHOWS THE DIFFERENCE. THIS LAST POINT THAT YOU MADE ABOUT THAT THE MEDICAL THERAPY IS THE BEST THAT WE KNOW AND IS IN BOTH ARMS OF THE TRIAL IS A GREAT ATTRIBUTION TO THAT, BECAUSE WE HAVE SEEN IN RESPONSE TO OUR REQUESTS FOR TRIALS TO LET DOCTORS DO WHAT THEY WOULD TYPICALLY DO, AND THE FACT THAT YOU'RE STACKING THE DECK IN A WAY AGAINST THE POSITIVE OUTCOME, YOU SHOULD BE COMMENDED.

DR. GARBER: I SECOND THAT. ETHAN.

00276

DR. BALK: I WANT TO ECHO SOMETHING SOMEBODY SAID A WHILE BACK. IF YOU THINK ABOUT THE STUDIES THAT ARE OUT THERE AND THE POINTS THAT WERE JUST MADE, MOST OF THEM ARE VERY SMALL, THEY'RE NOT GOING TO GIVE, OR ARE UNLIKELY TO GIVE CLINICAL RESULTS. SO IT'S ESSENTIALLY GOING TO BE THE CORAL STUDY IN SEVERAL YEARS TIME. WITH THAT ONE TRIAL, EVEN IF IT'S INCREDIBLE, A GREAT TRIAL, HIGHLY APPLICABLE, ET CETERA, ET CETERA, WE WOULD STILL NOT HAVE SAID THAT THERE WAS ROBUST EVIDENCE FOR ANYTHING BECAUSE IT'S ONE TRIAL.

DR. SCHWARTZ: WHAT ABOUT ASTRAL?

DR. BALK: WELL, THAT'S POSSIBLE, BUT IF YOU THINK THAT -- YOU KNOW, MOST OF THE CONVERSATION HAS BEEN FOCUSED ON CORAL. YOU KNOW, IT WILL BE INTERESTING TO SEE WHAT ASTRAL IS ABOUT ALSO, EVEN WITH ALL THE OTHERS. SO IF THEY BOTH COME OUT AND THEY SAY EXACTLY THE SAME THING IN BOTH OF THOSE STUDIES, THAT'S REALLY THE ONLY OPPORTUNITY FOR THERE TO BE ROBUST EVIDENCE, WHICH IS SOMEWHAT SIMILAR TO THE AHA/ACC GUIDELINES AT LEVEL 1, YOU STILL NEED A NUMBER OF TRIALS THAT ARE CONSISTENT. I JUST WANTED TO POINT THAT OUT.

DR. TEXTOR: I'M KIND OF ENTHUSED ABOUT ASTRAL. ASTRAL HAS A LOT, IT'S THE LARGEST TRIAL UP

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TO NOW. IF YOU LOOK AT THAT, THOUGH, THE TROUBLING FEATURE TO THAT ARE IDENTITY CRITERIA. I MEAN, BASICALLY (INAUDIBLE) SO THERE'S NOT A FIRM INDICATION FOR REVASCULARIZATION. THE CLINICIANS ARE UNCERTAIN AS TO WHAT TO DO. WELL, RANDOMIZE THEM. AND THEY'RE UNCERTAIN AND IT'S UNLIKELY THAT THEY WILL BE CERTAIN IN SIX MONTHS. THAT'S SORT OF AN IMPOSSIBLE THEORY AND I THINK IT'S ALMOST CERTAIN THAT WE'LL GET A GROUP OF PEOPLE WITH SUBCLINICAL LESIONS, AND I THINK THE REAL POTENTIAL DOWNSIDE IS THAT WE'LL GET TRIALS WITH INADEQUATE POWER.

DR. SCHWARTZ: (INAUDIBLE) IN THIS COUNTRY. THERE IS A BIG TENDENCY TO GO FOR INTERNATIONAL AND MULTINATIONAL TRIALS WHICH ARE GOOD TO SOME DEGREE, BUT I THINK IT'S BECOME INCREASINGLY DIFFICULT TO DO LARGE RANDOMIZED TRIALS IN THE UNITED STATES. A LOT OF COMMERCIAL INVESTIGATORS ARE FINDING IT'S EASIER AND FASTER TO DO THESE IN EUROPE IN PARTICULAR, AND WHILE THAT HAS, THAT HAS SOME GOOD ASPECTS TO IT, IT DOESN'T ALWAYS ADDRESS THE QUESTIONS IN THE WAY WE WANT THEM TO DO IT.

I THINK ONE OF THE THINGS, MARCEL, THAT NEEDS TO BE REVISITED BETWEEN NIH AND YOU GUYS, AND AHRQ OR FDA, IS TO LOOK AT WHAT'S HAPPENING WITH LARGE RANDOMIZED TRIALS IN THE UNITED STATES TO

FIGURE OUT A WAY TO REDEVELOP THAT INFRASTRUCTURE SO THAT WE CAN PLAY A LARGER ROLE, BECAUSE THAT'S ONE REASON WHY WE'RE GOING TO CONTINUE LACKING ANSWERS TO OUR SPECIFIC QUESTIONS.

YOU KNOW, THERE ARE CERTAIN THINGS THAT ARE USEFUL ACROSS THE WAY, BUT THERE ARE A LOT OF THESE ISSUES THAT ARE NOT QUITE DEFINED THE SAME WAY IN EVERY COUNTRY AND EVERY CULTURE.

DR. GARBER: OKAY, THANK YOU. DOES ANYBODY WANT TO MAKE ANY COMMENTS ON THE POINTS AT THE END ABOUT TRIALS? WE'VE ACTUALLY GOTTEN AROUND TO MOST OF THESE IN OUR DISCUSSIONS IN THE OTHER QUESTIONS ALREADY. THIS IS YOUR LAST CHANCE TO SPEAK.

MICHELLE HAS AN ANNOUNCEMENT AND THEN I'LL HAVE ONE.

MS. ATKINSON: I JUST WANTED TO SAY TO THE PANEL MEMBERS, THE SHUTTLE IS HERE TO TAKE EVERYBODY TO BWI. AND THEN ALSO FOR EVERYONE ELSE, IF YOU COULD PLEASE PICK UP YOUR TRASH, THERE'S TRASH CANS OUTSIDE. THANK YOU.

DR. GARBER: LET ME -- I WANT TO THANK THE SPEAKERS WHO ALL DID AN EXCELLENT JOB AND IT WAS EXTREMELY USEFUL TO US, BECAUSE YOU REPRESENTED DIVERSE PERSPECTIVES, AND YOU ALL CAME LOADED WITH

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FACTS, WHICH IS EXACTLY WHAT WE NEEDED FOR OUR DELIBERATIONS. YOUR PRESENTATIONS WERE RIGHT ON TARGET. I APOLOGIZE TO THOSE WHOM I CUT OFF, BUT THAT'S MY JOB AS CHAIR. I DON'T NECESSARILY RELISH CUTTING YOU OFF BUT I DO RELISH FINISHING ON TIME. AND THEN I WANT TO THANK THE PANELISTS FOR DOING AN EXCELLENT JOB. YOU WERE WELL PREPARED FOR THE MEETING, GREAT QUESTIONS, GREAT DELIBERATIONS. I APPLAUD YOU AND I'M SURE CMS DOES AS WELL.
IT'S BEEN A REAL HONOR AND PRIVILEGE TO BE CHAIR FOR THESE PAST TWO YEARS. AS A REGULAR MEMBER I WILL BE UNLEASHED, SO I CAN SAY WHAT I REALLY THINK, BUT I REALLY DO APPRECIATE EVERYTHING THAT YOU ALL HAVE DONE FOR ME. THANK YOU.
(APPLAUSE.)
DR. SALIVE: ON BEHALF OF CMS, I WANT TO THANK ALAN AGAIN FOR HIS STRONG TENURE AS CHAIR, AND I WANT TO THANK ALEX FOR HIS SERVICE AS VICE CHAIR. I WANT TO THANK ALL THE PANELISTS FOR COMING, AND I KNOW YOU ENDURED A LOT TO GET HERE, AND THANK YOU FOR ALL YOUR DELIBERATIONS.
WE WILL BE POSTING THE VOTING UP ON THE WEB SITE VERY SHORTLY AND ULTIMATELY WITHIN ABOUT A MONTH, WE DO POST THE TRANSCRIPT AS WELL, SO EVERYONE CAN LOOK FORWARD TO THAT.

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THE MEETING IS ADJOURNED.

(WHEREUPON, THE MEETING ADJOURNED AT 2:55 P.M.)

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