TEMPORAL TRENDS IN PERCUTANEOUS CORONARY INTERVENTION AND ASSOCIATED IMPACT ON CLINICAL AND PATIENT-REPORTED OUTCOMES

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Cardiovascular disease remains the leading cause of mortality and morbidity in the 21st century accounting for about one-fifth of deaths overall each year in the United States. Percutaneous coronary intervention (PCI), used initially in the 1970s, is now the most commonly performed non-surgical procedure for atherosclerotic coronary disease. PCI, in the last three decades, witnessed rapid advancements, both technologically (from balloons to stents and atherectomy devices) as well as in adjunct therapy (antithrombotics, fibrinolytics and antiplatelet agents). The purpose of this dissertation, designed as three research papers, was to capture this evolution and the associated impact on clinical and patient-reported outcomes, in the prospective, multicenter NHLBI-sponsored 1985-86 PTCA (era of balloon angioplasty) and 1997-2004 Dynamic (era of stents, brachytherapy and drug-eluting stents) registries.

Temporal trends in clinical practice revealed the heterogeneity in patients (and lesions) undergoing PCI and yet, consistent dramatic improvements were seen in procedural success with reduced need for repeat procedures; little impact was observed in one-year mortality rates. In the Dynamic Registry, significant reductions in one year prevalence and risk of patient-reported angina were observed concurrent to use of new evidence-based secondary pharmacological therapy. In contemporary practice, women and patients with prior/repeat PCI continued to be at high-risk for post-procedural symptoms. Supplemental therapy, following initial PCI, was more often pharmacological with concomitant reduction in bypass surgery and repeat PCI. On average,

patient-reported quality of life improved over time and was influenced by both symptom status and the need and type of supplemental therapy.

Indeed, these findings reflect the dynamic nature of PCI with an increasingly heterogeneous treatment population and yet favorable procedural outcomes (procedural success, reduced repeat procedures, greater relief of symptoms). More importantly, they highlight the continued lack of impact on mortality and identify symptom-prone subsets in contemporary practice. This time-sensitive documentation is especially fitting given the 300% increase in the number of PCIs since its initial use. From a public health point of view, any treatment modality applied in this magnitude warrants constant surveillance, more so with the emerging safety concerns, and this underscores the importance of well-designed registries.

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OVERVIEW AND OBJECTIVE

Cardiovascular disease (CVD) is the leading cause of mortality and morbidity, worldwide, and coronary artery disease (CAD) is the most common cause of CVD-related deaths. The advent of percutaneous coronary intervention (PCI) revolutionized treatment of CAD and is currently one of the most commonly performed non-surgical procedures, both in the U.S. and abroad. The field of PCI, per se, has seen rapid technological developments since its initial use in 1977 and this in turn, has widened the profile of patients and lesions undergoing the procedure.

The purpose of this dissertation, therefore, is to document evolution of PCI in over two decades of clinical practice and its associated impact on outcomes from perspective of both the provider (cardiologist) and the receiver (the patient). Specifically, the objectives of the three research papers are:

1. To document trends in patient, lesion, and procedural characteristics, and compare in-hospital and one year outcomes - from the era of balloon angioplasty (1985-86 PTCA registry) to that of stents (1997-2004 Dynamic registry).

2. To document trends in post-procedural angina, at one year of follow-up, across the four recruitment waves of the Dynamic registry, representing the advent (wave 1) and uniform use (wave 2) of bare metal stents, intra-coronary radiation (wave 3) and advent of drug-eluting stents (wave 4) and identify predictors of symptoms in contemporary practice.

3. To evaluate whether improvements in PCI has influenced the 'price' for achieving symptom-free status and the associated impact on patient-reported quality of life indicators.

BACKGROUND

CORONARY ARTERY DISEASE

CAD, the most common form of cardiovascular disease in adulthood, is a pathological condition in which there is obstruction to the blood flow in the coronary arteries that supply the heart. Deposition of atheromatous plaques in the coronaries results in narrowing of the vessel lumen reducing blood supply to the myocardium. The spectrum of clinical severity ranges from asymptomatic status to symptoms that include chest pain (angina), breathlessness (dyspnoea), fatigue, palpitations, and acute events including myocardial infarction (MI), congestive heart failure (CHF) and even death. The risk factors for CAD can be classified as modifiable and non-modifiable. Family history and sex belong to the non-modifiable category while lifestyle behaviors such as lack of physical activity, poor dietary habits and smoking are some of the modifiable ones. Co-morbid conditions such as obesity, hypertension, hyperlipidemia and diabetes are also known to increase the risk of CAD.

PUBLIC HEALTH BURDEN

CVD remains the leading cause of mortality and morbidity in the 21st century. In the United States, CVD is the leading cause of death for both men and women and across all races,

accounting for about one-fifth of deaths overall each year [1]. As of 2003, CVD was prevalent in 71,300,000 Americans, of whom 13,200,000 were reported to have CAD. Approximately 53% of CVD mortality was attributed to CAD followed by 18% for stroke. Although death rates from CAD declined 26.5% from 1992 to 2002, the actual number of deaths declined by only 9.9%; 83% of those who died from CAD were over 65 years of age.

Apart from the huge clinical impact, the financial burden associated with CVD is high with cost of CVD in 2005 estimated at $393.5 billion; the amount for CAD alone was $142.1 billion dollars [1]. Surveys conducted during 1987-2000, showed that among the top 15 most costly medical conditions, heart disease occupies first place with an 8.1% increase in total healthcare spending. These statistics provide compelling evidence of the impact of CAD on the society and the need to identify and assess effective preventive and treatment strategies. Although primary prevention is ideal, the pressure to treat the already prevalent disease burden is immense.

TREATMENT OF CORONARY ARTERY DISEASE

In addition to behavioral and risk factor management, the treatment options for CAD ranges from non-invasive pharmacological therapy to invasive revascularization procedures (coronary artery bypass grafting (CABG) and percutaneous interventions) [2].

Pharmacological therapy is often the first line of treatment and includes anti-anginal medications such as nitrates, beta-blockers and calcium channel blockers. In addition to these drugs, aspirin, an antiplatelet agent, has shown to be especially effective in early stages of MI and reduction of cardiovascular mortality [3]. Prior to the advent of percutaneous coronary

intervention (PCI), CABG was the only other alternative mode of CAD therapy. Saphenous vein grafts, harvested from the patient's legs and fashioned as conduits, were used to bypass coronary lesions to supply blood to distal portions. Randomized trials like the Veterans Administration (VA) study [4,] Coronary Artery Surgery Study (CASS) [5] and European Coronary Surgery Study [6,] compared medical therapy to surgical treatment and found that both options had similar survival benefits except in multivessel disease or poor ventricular function, wherein surgery was better. However, this benefit seen with CABG lasted for only 5-7 years after which symptoms returned with increasing risk of mortality [7]. This was attributed to degeneration of the vein grafts and prompted use of arterial conduits like the internal mammary artery, which is currently the conduit of choice.

Percutaneous Coronary Intervention

The concept of PCI was introduced in 1964 and balloon angioplasty was first performed to dilate a single lesion in a 38-yr old man in Switzerland in 1977 [8]. Ever since then and up to the approval of the first drug-eluting stents, this field has undergone rapid developments. In the year 2003, approximately 664,000 procedures were performed on 652,000 patients in the U.S., an estimated increase of more than 300% since 1987 (Appendix A) [1].

The beneficial effect of balloon angioplasty was attributed to stretching and tearing of the plaque, accompanied by its redistribution [9]. Although this resulted in initial success rates of 86-88%, complications such as abrupt vessel closure, due to dissection and / or thrombus [10], necessitated emergency surgery as a bail-out option. This prompted development of devices that could incise and/or remove plaques (cutting balloons, atherectomy devices), ablate lesions (Excimer angioplasty, brachytherapy) or serve as scaffolds (metallic stents) that prevent vessel

recoil. Of these, use of bare-metal stents (BMS) resulted in drastic reduction in acute complications, simultaneously increasing the success rates. However, they triggered thrombus formation and inflammatory responses resulting in restenosis that necessitated re-intervention. The latest in the armamentarium are drug-eluting stents (DES) – polymer-based stents with drug coating with immunosuppressant and antithrombotic properties. Numerous trials, conducted within a short time frame, showed dramatic improvements with restenosis rates as low as 0% [11, 12, 13]. Paralleling these technological developments, are improvements in adjunct therapy which include antiplatelets (aspirin, ticlopidine, clopidogrel) and anticoagulants (hirudin, bivalirudin and low-molecular weight heparin, glycoprotein IIb/IIIa platelet receptor inhibitors).

However, in spite of this progress, the field of PCI now appears to be at crossroads. Long term follow-up of the DES has unearthed concerns – increased risk of mortality and late stent thrombosis [14, 15] - that, if validated, could amount to a major public health burden. It has also brought to light, concerns of dual antiplatelet therapy use – their appropriate duration that depends on the stent type as well as patients' responsiveness and compliance to these medications. Overall, since initial use of the procedure, it appears that the profile of patients (and lesions) undergoing PCI has become quite heterogeneous, to the extent that almost half of the procedures today are performed under 'off-label' or 'untested' circumstances [16]. This, therefore, makes it vital to have a time-sensitive documentation of the evolving real world clinical practice and its associated impact, so as to provide the much-needed 'big picture', in the context of which future developments and concerns can be assessed.

NATIONAL HEART, LUNG AND BLOOD INSTITUTE (NHLBI)-SPONSORED 1985-86 PERCUTANEOUS TRANSLUMINAL CORONARY ANGIOPLASTY (PTCA) AND 1997-2004 DYNAMIC REGISTRIES

Randomized clinical trials (RCT) are considered the gold standard in evidence-based medicine. However, in a field such as PCI with rapid technological progress, new devices are often introduced after initiation of a RCT and are in widespread use by the time the findings are available. Therefore, when angioplasty became available for clinical use, the NHLBI set up the 1977-1981 PTCA registry to track use and performance of the procedure in the real world. Following the rapid uptake of the procedure by the medical community, this registry was reopened in 1985 [17, 18] to verify and quantify the progress in the field. This registry recruited and followed 2431 consecutive patients, with no prior revascularization, undergoing angioplasty PCI from 16 centers in North America and Canada (Appendix II – to be included). The findings from this 1985-86 PTCA registry demonstrated that procedural success of angioplasty had improved and the need for CABG had decreased, and called for a randomized trial to compare this procedure to CABG. This registry was also showed racial difference in cardiovascular risk profile of patients undergoing PTCA [19] and that women had significantly increased in-hospital mortality rates and angina at follow-up [20, 21].

Although during the PTCA registries, balloons were the only device available for use, the field witnessed extensive and rapid technological developments with the introduction of

atherectomy devices and bare metal stents. Given the pressing need to characterize contemporary practice, the Dynamic registry (DR) was developed in 1997 to recruit consecutive patients undergoing PCI in waves - 1: 1997-98, 2: 1999, 3: 2001-02, 4: 2004. This innovative design allowed for assessing safety and effectiveness in this rapidly changing field and included all catheter-based cases, regardless of whether it was first or repeat procedure. The registry recruited from 15-20 centers, of which 10 were from the 1985-86 PTCA registry (Appendix B). To allow sufficient representation of all the sites, enrollment of white males were discontinued when 120 white males were enrolled at a site or when 1,600 white patients were enrolled in the study as a whole. All consecutive minority and women patients were then recruited until 2,000 patients were enrolled across all sites. Recruitment was monitored by the Coordinating center, using screening logs, faxed to the center on a weekly basis. All research coordinators were trained in data collection procedures prior to patient enrollment. Written informed consent was obtained from participants to be contacted after discharge, and then annually, for health status information. Demographic information, medical history, angiographic and procedural details, and follow-up, information including repeat revascularization, were ascertained. The study protocol was approved by the Institutional Review Board of the University of Pittsburgh, the coordinating center, and all the sites involved.

1.0 TWENTY YEARS OF PERCUTANEOUS CORONARY INTERVENTION - THE EVOLUTION AND THE IMPACT. A REPORT FROM THE NHLBI-SPONSORED, MULTICENTER 1985-86 PTCA AND 1997-2004 DYNAMIC REGISTRIES

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1.1 ABSTRACT

Since its initial use, percutaneous coronary intervention (PCI) has witnessed rapid advancements in technology and adjunct therapy. The purpose of this analysis was to document this evolution and the associated impact on one year clinical outcomes. Temporal trend in de novo PCI was analyzed using consecutive cases in the NHLBI-sponsored 1985-86 PTCA registry and Dynamic registry (DR) waves: 1997-98 (bare metal stents), 1999 (uniform use of stents), 2001-02 (brachytherapy) and 2004 (drug-eluting stents). Patient and procedural profiles have expanded to include more elderly patients, those with concomitant comorbidities and rise in urgent procedures. Use of stents have increased over time from 70% in wave 1 (only bare metal) to 95% (72% drug-eluting) in wave 4; adjunct therapy including IIb/IIIa inhibitors (25% in wave 1 to 37% in wave 4) and antiplatelet agents (52% in wave 1 to 85% in wave 4) have been utilized more frequently. Despite the higher clinical severity in the stent era, procedural success and reduction in abrupt closures were achieved more often. Although little impact was observed on mortality rates, significant reduction was seen in 1-year adjusted risk estimates of late repeat PCI (hazard ratio: 0.7, 0.5, 0.5 and 0.3 for DR waves 1,2,3,4 compared to the PTCA registry) and death/myocardial infarction (hazard ratio: 0.7, 0.7, 0.6 and 0.7 for DR waves 1,2,3,4 compared to the PTCA registry). In the past two decades, PCI has evolved considerably to include more urgent, comorbid cases, yet achieving appreciable success rates with reduced need for repeat revascularization.

1.2 BACKGROUND

Percutaneous coronary intervention (PCI) is one of the most commonly performed non-surgical procedures, both in the U.S. [1] and worldwide [22, 23]. Ever since its initial use in the treatment of atherosclerosis [8], the field has witnessed rapid advancements, both technologically (from balloons to stents and atherectomy devices) as well as in adjunct therapy (antithrombotics, fibrinolytics and antiplatelet agents). Concomitantly, the profile of patients (and lesions) undergoing PCI in the last two decades, has become heterogeneous [24, 25]. The multicenter NHLBI-sponsored 1985-86 PTCA [26] and 1997-2004 Dynamic registries (DR) [24, 27] were specifically initiated to document this evolution and taken together, form a systematic and comprehensive source of prospective data, spanning two decades of real world practice. The purpose of our analysis, therefore, is two-fold – 1) to document trends in patient, lesion, and procedural characteristics, and 2) to compare in-hospital and one year outcomes - from the era of balloon angioplasty (1985-86 PTCA registry) to that of the stents (Dynamic registry). This time-sensitive appraisal is especially fitting at this juncture wherein the field is at the crossroads - restenosis, the long-time Achilles heel, may have been overcome [12, 13] , but there are emerging concerns of late stent thrombosis [14] and long-term safety [15].

1.3 METHODS

1.3.1 NHLBI-sponsored 1985-86 PTCA and 1997-2004 Dynamic Registries – design and data collection

The design and study population of the registries have been described in earlier reports [24,26,17,18]. Briefly, consecutive patients undergoing angioplasty for the first time were enrolled from 16 centers in the PTCA registry. The DR, developed in 1997, enrolled consecutive patients undergoing PCI, from 15-20 centers, in the following waves – 1: 1997-1998, 2: 1999, 3: 2001-02, 4: 2004; the cohort was enriched with oversampling of women and minorities. All research coordinators were trained in data collection procedures prior to patient enrollment and information on patient demographics, medical history, angiographic and procedural details, was ascertained. Standard definitions, as used in previous reports [18, 5], were applied and included the following: lesions were considered successfully treated when an absolute reduction of 20% in lesion severity and final diameter stenosis <50% was achieved; angiographic success was classified as either partial (some but not all attempted lesions successfully treated) or total (all attempted lesions successfully treated); procedural success was defined as achievement of either partial or total angiographic success without death, Q-wave myocardial infarction (MI), or emergency bypass surgery. For each cohort, the definition of MI was revised to match prevailing expert consensus - in the PTCA registry, it was defined as evidence of ≥ 2 of the following: (1) typical chest pain >20 minutes not relieved by nitroglycerin, (2) serial ECG recordings showing changes from baseline or serially in ST-T and/or Q-waves in ≥ 2 contiguous leads, or (3) serum enzyme elevation of CK-MB>5% of total CK (total CK>2x normal; LDH subtype 1>LDH subtype 2); in the DR, cardiac troponin levels was incorporated as a major criteria. Information

on major outcomes, over one year of follow-up, including death from any cause, MI, CABG, and repeat PCI (only non-staged procedures performed during a subsequent hospitalization) were available. In each cohort, hospital records were examined to ensure consistency with respective protocol definitions. Written informed consent was obtained from participants to be contacted after discharge, and then annually, for health status information. The study protocol was approved by the Institutional Review Boards of the coordinating center (University of Pittsburgh) and all the clinical sites involved.

1.3.2 Statistical Methods

For sake of comparability with the PTCA registry, the enriched subset (women and minorities) and patients with prior PCI in DR were not included in this analysis. Trends in baseline characteristics - patient, procedural, lesion-specific and in-hospital outcomes – were assessed across the cohorts using the Cochran-Armitage test for dichotomous variables [28] and the Jonckeheere-Terpsta test for continuous and nominal/ordinal variables [29]; continuous data were summarized as means and categorical variables as percentages.

One-year Kaplan-Meier (KM) estimates of event rates for death, combined death/MI, repeat PCI, CABG, and repeat revascularizations (repeat PCI+CABG), were compared using log rank statistics. Hazard ratios for the DR waves were assessed using Cox regression models with the 1985-86 PTCA registry as reference. Proportionality assumptions were assessed and found to be satisfied for death and death/MI, but not for repeat procedures. Therefore, repeat PCI, CABG and repeat revascularization were assessed at two time points – early (≤ 30 days) and late (31-365 days) - from index procedure. Patients, whose first repeat PCI or CABG occurred within 30 days from initial PCI, were censored for early events; analysis of late events included only those

who did not undergo any repeat procedure within the first 30 days. Baseline characteristics (available in all 5 cohorts), with significant trend across the waves, were evaluated for univariate associations with the events and those significant at the 0.05 level were included in multivariable models); baseline ejection fraction was not considered due to substantial missing data (35%). For the final model, for each event, the 'wave' variable, representing the cohorts, was forced to stay in the model and remaining covariates selected using standard stepwise procedure (Pentry $\leq$ 0.15, Pstay $\leq$ 0.10). All analyses were performed with SAS version 9.1 (SAS Institute Inc, NC).

1.4 RESULTS

1.4.1 Patient, lesion and procedural characteristics

Compared to the PTCA registry, higher percentages of women, older patients, those with concomitant comorbidities (hypertension, diabetes and severe non-cardiac conditions including peripheral vascular disease) and prior bypass surgery were observed in the stent era (Table 1.1).

Acute coronary syndrome (unstable angina/acute MI) remained the most common reason for revascularization over time, with a concomitant rise in non-elective procedures. The small yet increasing percentage of asymptomatic patients with evidence of CAD, undergoing PCI, is of note.

Baseline disease burden, as reflected by number of lesions and vessels diseased, was higher in DR waves, however, procedural attempts more often involved single lesions and native vessels (Table 1.1). The proportion of graft body interventions was also generally higher in the stent era (4-5% vs 3%, P_{trend} <0.01). Use of stents - either alone or in conjunction with balloons -

increased from 70% in wave 1 (only bare metal) to 95% in wave 4 (72% drug-eluting); rotational or directional atherectomy and brachytherapy were used in fewer than 2% of patients. Glycoprotein IIb/IIIa inhibitors, not available in the PTCA registry, were used more frequently in the early waves; the drop in use seen in Wave 4 coincided with the introduction of bivalirudin (wave 4: 28%). Procedural use of ticlopidine and /or clopidogrel increased to 85% in the latest wave (P_{trend} <0.001).

The profile of attempted lesions was more severe in the DR – treated lesions were more often located in a graft or were calcified or thrombotic (Table 1.2). Although the attempted lesions were more often located in the left anterior descending artery, a small but significantly higher proportion of left main lesions were observed in recent waves.

1.4.2 In-hospital outcomes and discharge medications

With the introduction of stents, procedural success was achieved and maintained more often (PTCA registry: 82%, wave 1: 94%, wave 2: 95%, wave 3: 96%, wave 4: 96%; P_{trend}: ≤0.001), despite treatment of more severe lesions. In contemporary practice, although complications such as local dissection and side branch occlusions were seen more often, significant reduction was observed in the rates of abrupt closures (Table 1.2). Trends in in-hospital events were also encouraging with a reduction in the rates of MI and CABG in the stent era; mortality rates were marginally, but not significantly higher in more recent cohorts (Figure 1.1).

Mean length of hospital stay was reduced from 4.1 days in 1985-86 to an average of 2.5 days in the DR (P_{trend} <0.001). Discharge rates of medications, including aspirin, beta-blockers and statins, recommended for secondary prevention of CAD, increased over time (Table 1.3).

1.4.3 One year events

While the advent of stents coincided with an increase in crude one-year mortality rates, cumulative rates of death/MI did not vary significantly between the five cohorts (Figure 1.2). Similar pattern was observed in unadjusted risk estimates at one year – mortality risk was significantly higher and risk of death/MI was non-significantly lower for the DR waves, when compared to the PTCA registry (Table 1.4). However, adjustment for baseline cohort differences resulted in a significant reduction in combined mortality / MI risk in contemporary practice. Secondary univariate analysis of mortality was performed in selected subgroups. Crude 1-yr mortality rates, among 'urgent cases, decreased over time (PTCA registry: 7%, wave1: 5%, wave 2: 4%, wave 3: 5%, wave 4: 3%; $P_{logrank}$: 0.08), and among those with AMI, mortality risk at one year was non-significantly lower for the more recent waves (hazard ratios: 1.1, 1.0, 0.6, 0.9 for waves 1,2,3,4 compared to the PTCA registry). In the DR, use of stents was associated with lower mortality rates at one year (5% vs 7%, $P_{logrank}$: 0.02).

Although the overall 1-yr rates of repeat revascularization (repeat PCI or CABG) were reduced from 29% in the PTCA registry to 11% in Wave 4, analyses by post-discharge interval revealed an interesting pattern. While the reduction in early CABG rates was initially steep, and plateauing thereafter, need for late CABG successively reduced over time (Figure 1.3). Risk of CABG for the DR waves, compared to the PTCA registry, was significantly lower within and after 30 days from initial PCI (Table 1.5). On the other hand, while cumulative rates of early repeat PCI significantly increased over time, need for late repeat PCI was significantly reduced across the cohorts (Figure 1.3). Risk of repeat PCI for DR waves, compared to the PTCA registry, followed similar pattern, both before and after adjustment for baseline differences (Table 1.5). Secondary analysis was performed in only those patients in whom both total

angiographic and procedural success was achieved. The pattern of risk for repeat PCI remained similar to that seen in the overall cohort, i.e., need for early repeat PCI was higher and that for late repeat PCI was lower for patients in the Dynamic registry, when compared to those in the PTCA registry.

1.5 DISCUSSION

Our report gives a time-sensitive appraisal of PCI and associated outcomes spanning two decades of clinical practice in real-world consecutive patients. In contemporary practice, the high procedural success with improved effectiveness (reduced need for repeat PCI) at one year are especially noteworthy, given the widening patient and procedural profile. Although little impact was observed on mortality alone, the risk of death or MI was significantly lower and indicative of improved safety over time.

1.5.1 The patient, lesion and procedure

Technological improvements in the field of PCI were expected to widen the scope and feasibility of the procedure, and our report confirms this in a twenty-year snapshot of clinical practice. In contrast to the early days when PCI was primarily applied to discrete de novo lesions, the field has progressed to more challenging grounds, including older patients, with concomitant comorbidities, for acute MI, vein graft and calcified lesions. Angioplasties, these days, are also being performed under more emergent / urgent circumstances, when compared to the pre-stent era. As demonstrated in previous reports [24, 27], revascularization, at both the vessel and lesion

level, was mostly selective, despite the greater disease burden seen at entry. The concept of complete anatomic revascularization stemmed from early CABG studies, which was then extended to the field of PCI. However, with more percutaneous procedures being performed for acute conditions, functional revascularization may be of greater immediate priority. It is also possible that, given the increasing proportion of older patients, baseline angiographic disease may be predominantly diffuse, permitting only partial rather than complete revascularization.

1.5.2 In-hospital outcomes

The heterogeneity of patients and lesions being treated over time is expected to impact procedural outcomes. When stents were initially introduced, indications widened to include complex lesions and were likely to be associated with high rates of distal embolization, dissections, and side branch occlusions [27, 30]; subsequent reduction in these rates was attributed to improved operator technique and patient selection, facilitated by use of adjunct antithrombotic or fibrinolytic agents. Our report reconfirms this, wherein, angiographic / procedural success were achieved and maintained more often in the stent era, in addition to the overall low risk of immediate complications and reduced need for emergency CABG.

1.5.3 Post-procedural mortality or MI

Previous studies in PCI have demonstrated lack of impact on long-term all-cause mortality [24, 31,32] and this has remained a matter of scientific inquiry. Other reports have shown a favorable impact on mortality and MI in high-risk settings such as acute MI [33, 34, 35 and cardiogenic shock 36,37,38]. In our analysis, cumulative mortality rates increased with the advent of stents and plateaued

thereafter, with higher unadjusted risk estimates for the more recent waves. However, given the severity of patients and lesions treated in the latter waves, it is encouraging that there was no significant impact on mortality. Additionally, as seen in our univariate analyses, mortality tended to be lower among urgent cases and those treated for AMI. Detailed risk-adjusted analysis is warranted in these subsets to delineate extent of improvement over time. The importance of monitoring cause-specific mortality has also been highlighted in recent report of long-term safety concerns with DES use [15]. It would therefore, be interesting to assess impact on cardiac/non-cardiac mortality ratio over time.

In contrast to the trend in mortality alone, the impact on the combined endpoint of death or MI has been favorable and probably driven by MI. In the early days, PCI-related infarction was mostly attributed to abrupt closures and acute stent thrombosis. Stents were primarily designed to counteract vessel recoil and circumvent acute closure, and our data supports this. Additionally, the availability /use of improved adjunct drug regimen, including aspirin and clopidogrel, may have conferred added advantage.

1.5.4 Repeat revascularization

Improvements in PCI have been primarily aimed at reducing the need for repeat revascularization and as seen in our report, this depends on the post-discharge interval. Need for repeat PCI, within 30 days of index procedure, was higher in the stent era, albeit low absolute rates. In addition to reduced hospital stay, this could also represent a shift in favor of PCI, seen from the balloon era, where the only alternative to a failed initial PCI was CABG. On the other hand, a previous analysis of combined endpoint of 30-day events (including repeat target vessel PCI), showed very little improvement in the rates across the first three DR waves; factors that

were associated with higher risk included multivessel disease, acuity, ostial lesions and pulmonary disease [39].

The sustained reduction in the need for late repeat revascularization – repeat PCI or CABG – is what truly underscores the progress made in the field. The cohorts in this report are representative of advancements in PCI at the respective time periods – new devices, adjunct therapy, and improved antiplatelet regimen. The reduction in need for late PCI, observed when the analysis was restricted to patients with initial success– angiographic and procedural, is further proof for the favorable impact of the evolution in PCI.

In addition to improvements in PCI, the role of concomitant pharmacological therapy cannot be overlooked. In the last two decades, a rise in the use of aspirin, beta blockers, plaque-stabilizing/ regressing agents like statins and clopidogrel have been observed at discharge. There is greater need for their extended use and compliance, given the emerging concerns of disease progression [40] and stent thrombosis [41].

1.5.5 Limitations

Data for the analyses is obtained from a registry database - a design considered less rigorous than randomized trials (RCT). However, strict inclusion criteria in trials often lead to exclusion of patients with high-risk characteristics known to impact procedural outcome. The trial protocols often do not allow for premature antiplatelet/medication discontinuation, circumstances commonly encountered in the real world. Thus, prospective enrollment of consecutive cases, as in our registries, permits better representation of contemporary practice with immediate applicability of results. RCTs are also designed for proving efficacy of treatments while registries help with the evaluation of safety and effectiveness, an example of which is the issue

of DES-related thrombosis [42] that was identified using registry data, with no prior evidence in early trials [12,13]. Model-building included only data available in all five cohorts, and information on bifurcations, ostial lesions and other lesion morphology were not used. Data on lifestyle modifications, bleeding complications, and medication dose were also not routinely collected.

1.6 CONCLUSION

In the past two decades, initial PCI has evolved considerably to include more urgent cases and higher percentage of patients with concomitant comorbidities, and yet achieved and maintained high success rates, with improved effectiveness (reduced need for repeat procedures) at one year. Extended follow-up is necessary to evaluate the duration of these benefits especially in clinically challenging subsets that include chronic total occlusions, bifurcation lesions, and patients with diabetes. Further research is also warranted to assess whether the observed trend in clinical success has been translated to improved symptom relief and quality of life of the patients.

Table 1.1: Trends in patient demographics and procedural characteristics in the NHLBI-sponsored PTCA (1985-86) and Dynamic (1997-2004) registries

	PTCA	Dynamic Registry			
	Registry (N=2431)	Wave 1 (N=1557)	Wave 2 (N=1250)	Wave 3 (N=1212)	Wave 4 (N=1283)
Patient demographics					
Age > 65 years, % ‡	28	42	45	48	47
Women, % ‡	26	32	32	35	31
Race, % ‡					
White	92	86	87	88	84
Black	4	5	8	7	12
Asian	1	3	3	3	3
Hispanic	1	7	6	4	6
Mean BMI, kg/m^2 ‡	27.0	28.2	28.6	29.1	29.0
Prior MI , % ‡	38	33	23	17	15
History of CHF, % †	6	8	7	10	8
History of Diabetes, % ‡	14	26	25	26	31
Severe concomitant non-cardiac disease, % ‡	6	29	32	36	37
Prior CABG, % ‡	11	12	14	14	16
Smoking, % ‡					

Table 1.1 continued

Current	31	29	29	25	23
Former	40	38	40	41	40
Ejection fraction, mean ‡	58.0	55.3	53.1	51.9	52.2
Primary Reason for Revascularization, % ‡					
Stable Angina	38	25	21	19	20
CCSC I/II	17	12	6	8	10
CCSC III/IV	20	12	6	6	5
Unstable Angina /Acute MI	58	66	72	69	68
Cardiogenic shock	n/a	2	2	3	2
Thrombolytic therapy‡	4	6	10	9	7
Asymptomatic CAD / Other	4	9	7	12	12
Procedural details					
Procedural circumstance, % ‡					
Elective	75	63	55	49	54
Urgent	19	24	31	38	32
Emergent	6	13	14	13	14
Baseline significant lesions, mean ‡	2.6	2.7	2.7	2.9	3.1
Number of lesions attempted, % ‡					
1	63	68	69	68	72
2	25	24	24	24	23
≥ 3	12	8	8	8	5

Table 1.1 continued

Baseline vessel disease, % ‡					
Single	48	46	47	40	36
Double	32	32	30	33	32
Triple	21	22	23	28	33
Number of vessels attempted, % ‡					
1 native vessel	77	84	83	83	81
2 native vessels	17	10	10	10	14
3 native vessels	2	0.6	0.7	0.9	0.3
Graft only	3	4	5	5	4
≥ 1 native vessel and graft	1	1	1	0.7	1
Overall balloon use, % ‡	100	97	92	80	79
Overall stent use, % ‡	n/a	70	85	94	95
Gp IIb/IIIa inhibitors prior or during procedure, % ‡	n/a	25	34	55	37
Clopidogrel and/or ticlopidine 24 hours prior or during procedure, % ‡	n/a	52	43	65	85

BMI: Body mass index, CCSC: Canadian cardiovascular society classification; MVD: multivessel disease; n/a: not available; P_{trend} in characteristics across the cohorts: * ≤ 0.05, † ≤ 0.01, ‡ ≤ 0.001, assessed using Cochran Armitage test for 2-level categories and Jonckeheere-Terpsta test for continuous variables and nominal / ordinal categories

Table 1.2: Characteristics of attempted lesions and angiographic outcome in the NHLBI-sponsored PTCA (1985-86) and Dynamic (1997-2004) registries

	PTCA	Dynamic Registry			
	Registry (N=3791)	**Wave 1 (N=2218)**	**Wave 2 (N=1755)**	**Wave 3 (N=1728)**	**Wave 4 (N=1720)**
Location, % ‡					
Right coronary artery	29	34	35	34	32
Left main	0.4	0.9	0.7	1	1
Left anterior descending	46	39	36	38	38
Left circumflex	21	22	22	22	24
Graft	3	5	6	5	5
Diameter stenosis, % ‡					
< 50%	2	2	2	1	0.2
50-70%	15	10	12	9	5
70-90%	37	31	35	39	49
90-99%	34	41	39	40	34
Total occlusion	2	16	13	11	12
Lesion Characteristics					
Evidence of thrombus ‡	11	22	24	18	17
Calcified ‡	11	30	27	24	27
Receives collaterals ‡	21	14	14	10	10

Table 1.2 continued

Supplies collaterals	8	6	4	4	10
Final % stenosis, mean ‡	33	12	9	6	5
Angiographic success, %	81	94	95	95	96
Complications, %					
Dissection ‡	3	12	5	2	3
Side branch occlusion	0.4	3	2	2	2
Abrupt closure (in lab) ‡	3	2	1	0.3	0.2

P_{trend} in characteristics across the cohorts: * ≤ 0.05, † ≤ 0.01, ‡ ≤ 0.001, assessed using Cochran Armitage test for dichotomous variables and Jonckeheere-Terpsta test for continuous variables and nominal / ordinal categories

Table 1.3: Trends in duration of hospital stay and discharge medications, among those alive at discharge, in the NHLBI-sponsored PTCA (1985-86) and Dynamic (1997-2004) registries

	PTCA	Dynamic Registry			
	Registry (N=2397)	Wave 1 (N=1527)	Wave 2 (N=1228)	Wave 3 (N=1194)	Wave 4 (N=1258)
Mean length of Stay, days ‡	4.1	2.7	2.6	2.4	2.2
Discharge Medication, %					
Aspirin ‡	84	94	94	95	97
ACE inhibitor ‡	1	29	37	45	54
Beta blocker ‡	26	66	72	77	81
Calcium channel blocker ‡	78	30	21	17	14
Statins ‡	n/a	33	54	70	83
Digitalis	6	6	7	6	4
Diuretics ‡	6	15	18	20	24
Long-acting nitrates ‡	34	33	27	21	13
Ticlopidine ‡	n/a	70	23	1	1
Clopidogrel ‡	n/a	n/a	61	92	95
Warfarin ‡	4	5	6	9	8

N/a: not available. P_{trend} in characteristics across the cohorts: * ≤ 0.05, † ≤ 0.01, ‡ ≤ 0.001, assessed using Cochran Armitage test for dichotomous variables and Jonckeheere-Terpsta test for continuous variables and nominal / ordinal categories.

Table 1.4: Risk of Death and Death / MI at one year for the NHLBI-sponsored 1997-2004 Dynamic registry (reference: 1985-86 PTCA registry)

	Death (N=345)		Death / MI (N=730)	
	HR	**95% CI**	**HR**	**95% CI**
Unadjusted				
PTCA Registry	1.00	reference	1.00	reference
DR Wave 1	1.53†	1.12-2.09	0.96	0.78-1.18
DR Wave 2	1.51†	1.09-2.09	0.96	0.77-1.20
DR Wave 3	1.43*	1.02-2.01	0.88	0.70-1.11
DR Wave 4	1.57†	1.14-2.15	1.00	0.80-1.23
Adjusted§				
PTCA Registry	1.00	reference	1.00	reference
DR Wave 1	0.92	0.64-1.33	0.67‡	0.53-0.85
DR Wave 2	0.96	0.66-1.40	0.68†	0.53-0.88
DR Wave 3	0.77	0.51-1.16	0.59‡	0.45-0.78
DR Wave 4	0.89	0.60-1.32	0.69†	0.54-0.89

Table 1.4 continued

P value: * ≤ 0.05, † ≤ 0.01, ‡ ≤ 0.001;

§ Covariates included for adjusted estimates are listed below, by type of event:

Death: Age<65, body mass index, smoking status, history of congestive heart failure, diabetes, hypercholesterolemia, primary reason for revascularization, procedural circumstances, severe non-cardiac comorbidities, multivessel disease, attempt of total occlusion and proximal left anterior descending artery disease, overall balloon use; **Death/MI:** Age >65 years, body mass index, history of congestive heart failure, diabetes, primary reason for revascularization, procedural circumstances, and attempt of lesions with evidence of thrombus, calcified, receiving collaterals or in vein grafts

Table 1.5: Risk of Early (≤30 days) and Late (31-365 days) repeat revascularization for the NHLBI-sponsored 1997-2004 Dynamic Registry (reference: 1985-86 PTCA registry)

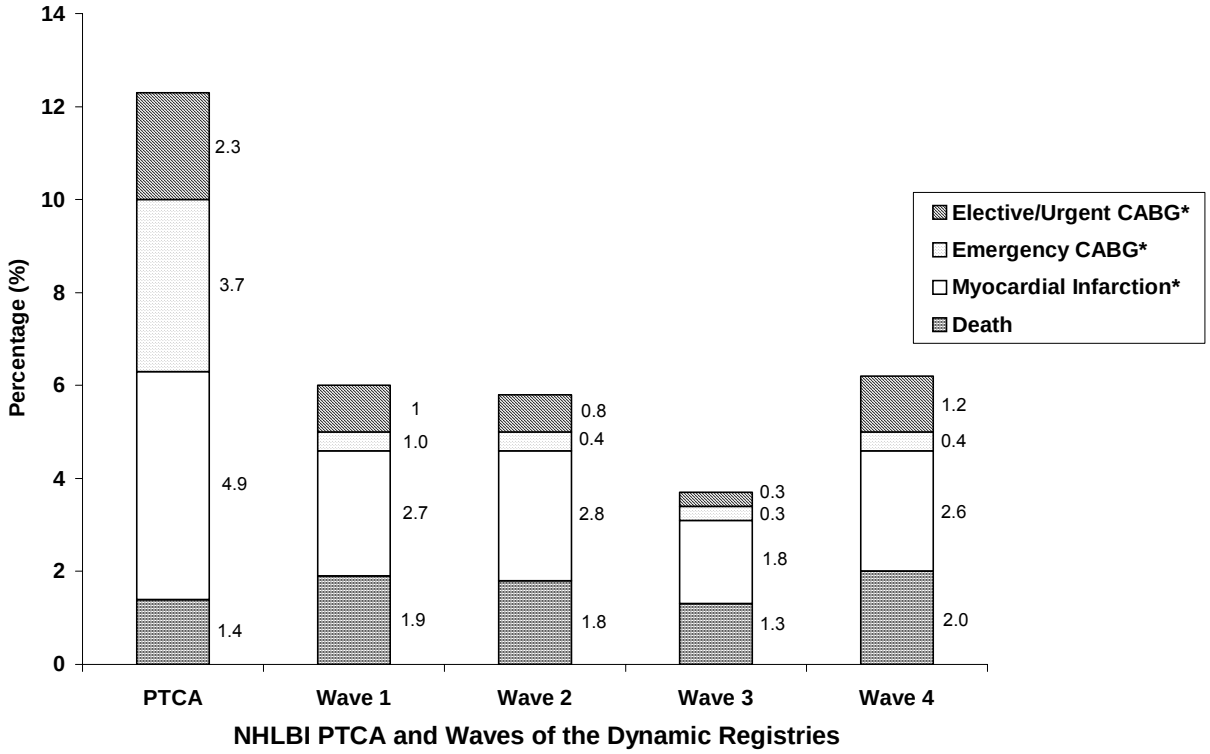
	Repeat PCI				CABG				CABG / Repeat PCI			
	Early (N=92)		**Late** (N=833)		**Early** (N=243)		**Late** (N=286)		**Early** (N=333)		**Late** (N=1016)	
	HR	**95% CI**	**HR**	**95% CI**	**HR**	**95% CI**	**HR**	**95% CI**	**HR**	**95% CI**	**HR**	**95% CI**
Unadjusted												
PTCA	1.00	reference	1.00	reference	1.00	reference	1.00	reference	1.00	reference	1.00	reference
DR Wave 1	2.43†	1.32-4.48	0.66‡	0.55-0.79	0.26‡	0.18-0.40	0.83	0.61-1.11	0.49‡	0.36-0.66	0.66‡	0.56-0.78
DR Wave 2	1.41	0.68-2.93	0.45‡	0.36-0.56	0.23‡	0.14-0.36	0.68*	0.48-0.94	0.33‡	0.22-0.48	0.48‡	0.39-0.58
DR Wave 3	2.34†	1.22-4.51	0.54‡	0.44-0.68	0.13‡	0.07-0.24	0.38‡	0.25-0.59	0.31‡	0.21-0.47	0.47‡	0.40-0.60
DR Wave 4	2.15*	1.14-4.07	0.32‡	0.25-0.41	0.25‡	0.16-0.39	0.22‡	0.13-0.36	0.42‡	0.30-0.59	0.29‡	0.23-0.37
Adjusted §												
PTCA	1.00	reference	1.00	reference	1.00	reference	1.00	reference	1.00	reference	1.00	reference
DR Wave 1	2.25†	1.22-4.16	0.72‡	0.60-0.87	0.23‡	0.15-0.34	0.82	0.61-1.10	0.39‡	0.28-0.53	0.72‡	0.60-0.85
DR Wave 2	1.29	0.62-2.68	0.50‡	0.39-0.62	0.21‡	0.13-0.34	0.67*	0.48-0.93	0.27‡	0.18-0.41	0.52‡	0.43-0.64
DR Wave 3	2.00*	1.04-3.87	0.58‡	0.47-0.73	0.11‡	0.06-0.22	0.37‡	0.24-0.58	0.26‡	0.17-0.39	0.52‡	0.42-0.64
DR Wave 4	1.78	0.93-3.41	0.35‡	0.27-0.45	0.22‡	0.14-0.34	0.19‡	0.11-0.32	0.33‡	0.23-0.47	0.31‡	0.24-0.39

Table 1.5 continued

HR: hazard ratio; CI: confidence interval, P value: * ≤ 0.05, † ≤ 0.01, ‡ ≤ 0.001.

§ Covariates included for adjusted estimates are listed below, by type of event:

Early Repeat PCI: Multivessel disease (MVD) and primary reason for revascularization; **Late Repeat PCI:** Age >65 years, primary reason for revascularization, evidence of thrombus, number of lesions and vessels attempted; **Early CABG:** Previous CABG, multivessel disease, circumstances of procedure, number of lesions attempted, total occlusion attempted, and proximal LAD lesion; **Late CABG:** History of Diabetes, MVD, and proximal LAD lesion; **Early Repeat PCI/CABG:** MVD, primary reason for revascularization, procedural circumstances, calcified lesion, total occlusion attempted, and proximal LAD lesion attempted; **Late Repeat PCI/CABG:** Age > 65 years, history of diabetes, MVD, primary reason for revascularization, evidence of thrombus, number of lesions attempted, proximal LAD lesion attempted, and vein graft attempted



* P_{trend} <0.001, assessed using Cochran Armitage test

Figure 1.1: Trends in in-hospital outcomes in the NHLBI-sponsored PTCA (1985-86) and Dynamic (1997-2004) registries

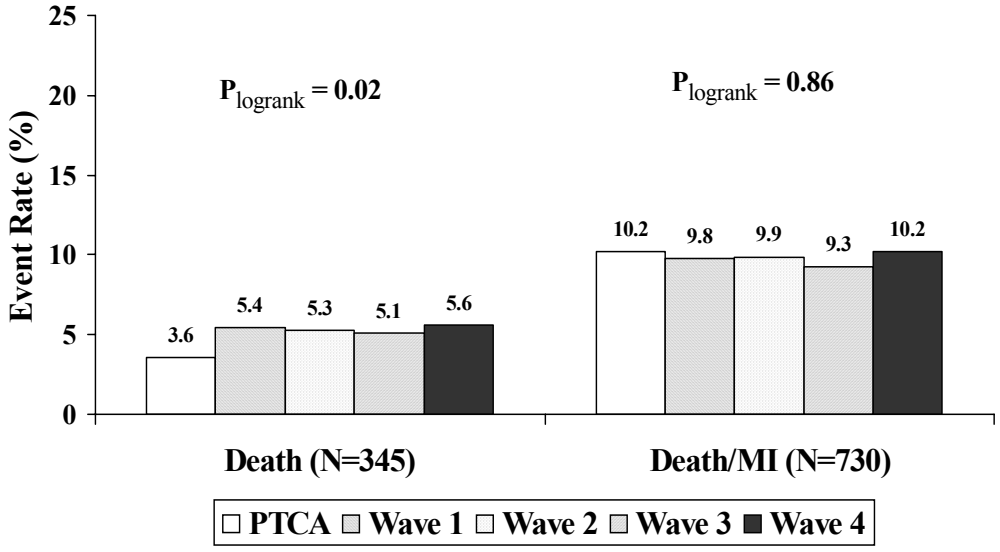
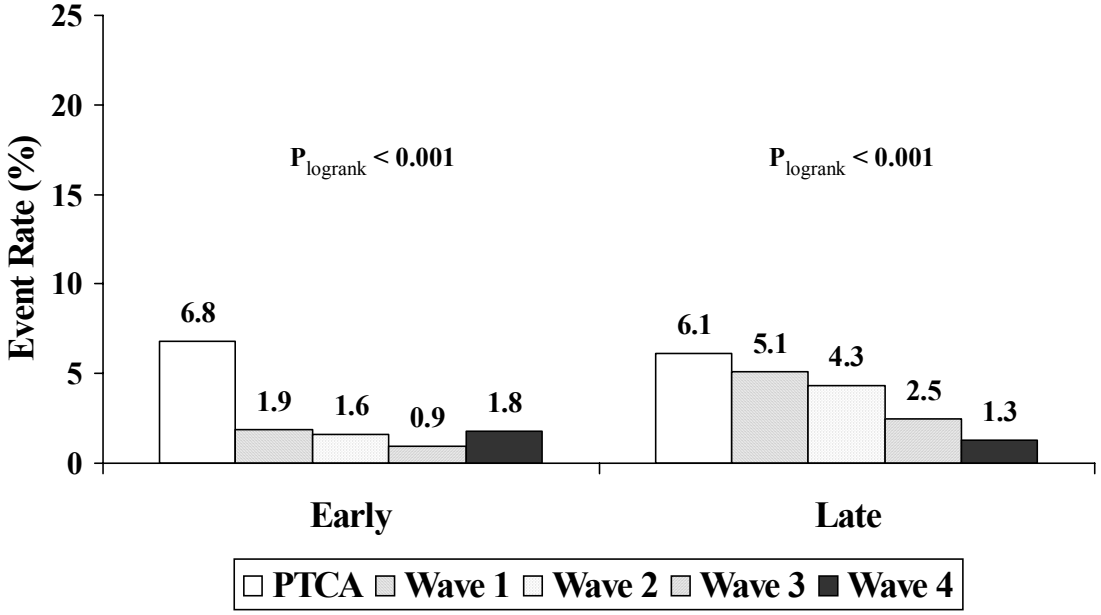


Figure 1.2: Cumulative (Kaplan Meier) event rates for Death and Death/MI in the NHLBI-sponsored PTCA (1985-86) and Dynamic (1997-2004) registries at one year

(A) Early (≤ 30 days) and Late (31-365 days) CABG



(B) Early (≤ 30 days) and Late (31-365 days) Repeat PCI

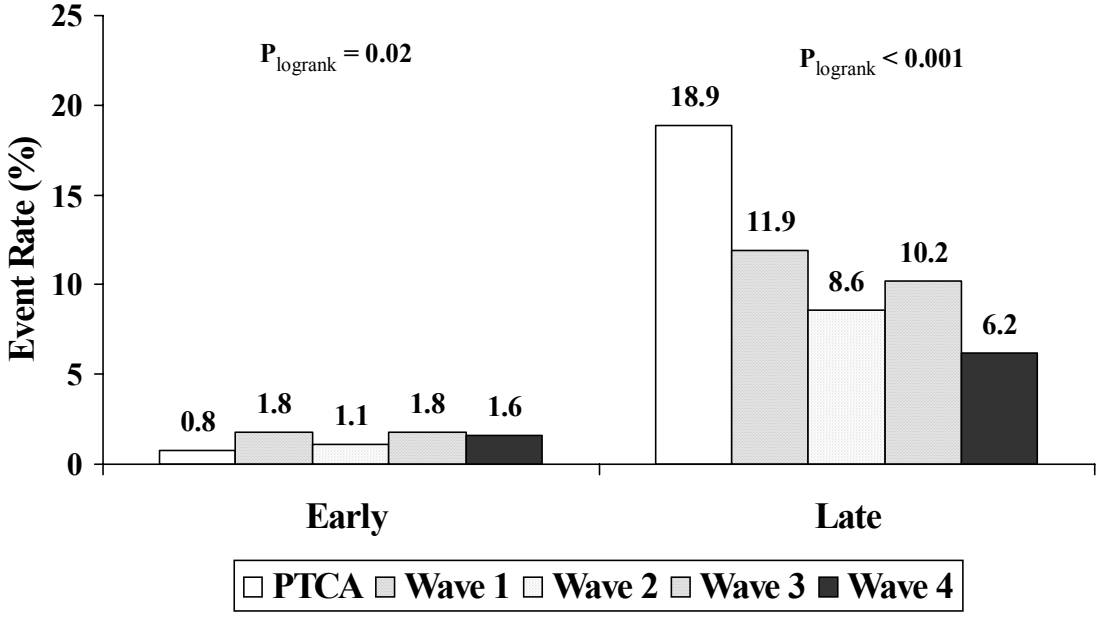


Figure 1.3: Cumulative (Kaplan Meier) event rates for early (≤ 30 days) and late (31-365 days) CABG (A) and repeat PCI (B) in the NHLBI-sponsored PTCA (1985-86) and Dynamic (1997-2004) registries

2.0 TEMPORAL TRENDS IN POST-REVASCULARIZATION ANGINA AND ITS PREDICTORS IN CONTEMPORARY PRACTICE: A REPORT FROM THE NHLBI-SPONSORED 1997-2004 DYNAMIC REGISTRY

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2.1 ABSTRACT

Evolution of percutaneous coronary intervention (PCI) with associated impact on clinical outcomes is well-documented. Our objective is to document temporal trends in post-procedural symptoms in patients sequentially enrolled in the NHLBI-sponsored Dynamic Registry (N in waves-1:2010, 2:1633, 3:1512, 4:1846). At 1-year follow-up, the percentage of consecutive patients (N: 6246) reporting angina of any severity in the past 6 weeks decreased from 24% in wave 1 to 20% in wave 4 (P_{trend}:<0.001). Evidence suggestive of interaction with PCI era was seen with large reduction in angina rates for patients with prior MI, diabetes, lack of initial procedural success, procedural use of anti-platelet agents and those discharged on ≥ 2 medication classes (beta blockers, long-acting nitrates, calcium-channel blockers, ACE-inhibitors). In contrast, difference in angina rates by history of prior PCI widened over time. Risk of post-PCI angina was lower for recent cohorts, even after adjusting for age, sex, race, primary reason for PCI, prior bypass or PCI, smoking status, comorbidities, repeat PCI, use of stent and ≥ 2 medication classes [relative risk (95% CI): 1.0 (0.9-1.1), 0.7 (0.7-0.8), 0.8 (0.7-0.9) for waves 2,3,4, compared to wave 1]. In the drug-eluting stent era (wave 4), significant predictors of post-PCI angina included female sex, prior bypass, prior or repeat PCI, and one-year MI. In conclusion, favorable temporal trends are seen in prevalence and risk of post-PCI angina, paralleling the evolution of the field in the last three decades. In contemporary practice, specific subgroups remain at high risk for symptoms and warrant closer attention.

2.2 BACKGROUND

Symptom relief and prolongation of life remain the primary goals of cardiovascular therapy. Percutaneous coronary intervention (PCI) has evolved rapidly in the past two decades and while the associated favorable impact on clinical success (high procedural success rates and reduced need for repeat revascularization) has been well-documented [24, 27, 43], there are few reports on the impact on post-procedural symptoms. More importantly, given the lack of demonstrable mortality benefit, there is an important need to focus on symptom-related patient outcomes following revascularization. The NHLBI-sponsored Dynamic registry enrolled consecutive patients undergoing PCI in 4 sequential waves from 1997 to 2004 [24, 44]. The registry represents significant phases in PCI evolution and can, therefore, provide insight into prevalence of post-PCI angina over time. The purpose of this report, therefore, is to 1) document temporal trends in patient-reported one year post-PCI angina and, 2) identify significant predictors of angina in contemporary practice (wave 4).

2.3 METHODS

2.3.1 The NHLBI-sponsored 1997-2004 Dynamic Registry

Consecutive patients undergoing PCI were sequentially enrolled in recruitment waves: Wave 1: 1997-98, Wave 2: 1999, Wave 3: 2001-2002, and Wave 4: 2004; each cohort was enriched (oversampled) with women and minorities [24, 44]. Baseline information on patient and procedural characteristics were ascertained by research coordinators trained in data collection. Written

informed consent was obtained from participants at baseline for enrollment and follow-up contacts. Patients were contacted by telephone, mail or during clinic visits, at one year of follow-up, and information on angina and medication use, in the past 6 weeks, was obtained. Hospitalizations for angina, myocardial infarction (MI), bypass surgery (CABG), and repeat PCI over one year were also recorded. The study protocol was approved by the Institutional Review Board of the University of Pittsburgh and those of all sites involved.

Stable angina was defined as pain precipitated by exertion and relieved by rest and/or sublingual nitroglycerin, with no change in pattern or severity within 6 weeks before intervention (baseline) or in the previous 6 weeks (follow-up). Unstable angina was defined as either pain presenting at rest, or exertional pain of at least Canadian Cardiovascular Society (CCS) Class III that began or increased in severity at least one CCS Class in the 2 months before intervention of follow-up. Acute MI, in the first 2 waves, was defined by the documented presence of ≥2 of the following criteria: clinical symptoms, enzyme-level elevations, new wall-motion abnormalities, and ≥2 serial electrocardiogram tracings showing changes from baseline or serially in ST-T and/or new Q waves in ≥2 contiguous leads; for waves 3 and 4, diagnosis of MI was based on either biochemical evidence of necrosis or serial ECG changes. Attempted lesions were considered complex if ≥ 1 of the following features were present: evidence of thrombus, calcified, at bifurcation, chronic total occlusions (occlusions in patients undergoing PCI for reasons other than MI), and ostial lesions [30].

Overall 8788 patients were enrolled in the registry and ~ 90% consented for follow-up. The present analysis excludes 297 patients who died within one year (% by waves: 3.5, 5.3, 5.0, 2.2; P_{trend}: 0.07) and 131 patients with no follow-up information (% by waves: 1.1, 1.4, 3.6, 1.5; P_{trend}: 0.02). To ensure generalizability, prevalence rates at follow-up were calculated using

consecutive patients only (N=6246) so that the enriched sample of women and minorities, recruited after the registry was closed to white men, were not included. Risk of follow-up angina for all waves, as well as significant predictors specific to wave 4 only (the most current wave) was based on all patients (N=7001) including the enriched subset.

2.3.2 Statistical Methods

Follow-up angina rates in consecutive patients are summarized by waves of enrollment and temporal trends – overall and by baseline characteristics - assessed using the Cochran-Armitage test for dichotomous variables [28] and the Jonckeheere-Terpsta test for continuous and nominal/ordinal variables [29]. In subgroup analyses, the possible differential effect of patient and procedural characteristics on the occurrence of angina over time was modeled using interaction term with recruitment wave in logistic regression models; $P \leq 0.15$ was considered suggestive of interaction. Relative risks (unadjusted and adjusted) of post-PCI angina, with wave 1 as the referent category, were estimated using generalized linear models specifying the binomial distribution and log link function (PROC GENMOD in SAS). For multivariate adjustment, baseline factors that significantly differed across the cohorts ($P_{trend} \leq 0.05$) and were also associated with follow-up angina ($P \leq 0.10$) were considered. For the final model, recruitment wave was included with a stepwise selection ($P_{entry} \leq 0.10$, $P_{stay} \leq 0.05$) method used to select other significant covariates. To assess the impact of missing angina information, sensitivity analyses were performed by assigning symptomatic status to patients 1) alive but missing information and, 2) who died over one year.

Significant predictors of post-PCI angina, in contemporary practice (wave 4), were identified using only baseline symptomatic patients (primary reason for index PCI: stable or

unstable angina or acute MI), for comparability with previous report [45]. Sequential models were fit using stepwise selection methods and log binomial regression analysis. The first adjusted model included baseline patient and procedural characteristics. The second adjusted model included Model 1 variables and statistically significant in-hospital and one-year characteristics, including intercurrent adverse events and repeat revascularization. All analyses were performed with SAS version 9.1 (SAS Institute Inc, NC).

2.4 RESULTS

Compared to 1997-98 (wave 1), patients in the latter waves were older, had more comorbidities (hypertension, diabetes and severe non-cardiac conditions) and prior revascularization (PCI or CABG) (Table 2.1). Although number of diseased vessels / lesions, at baseline, increased over time, procedural attempts more often involved single vessels / lesions. Overall stent use increased over time (66% to 93%), with 75% of wave 4 patients receiving a drug-eluting stent. Over time, there was more frequent use of glycoprotein IIb/IIIa inhibitors (wave 1: 23%, wave 2: 32%, wave 3: 52%, wave 4: 35%, P_{trend}: <0.001), and antiplatelets (ticlopidine or clopidogrel, wave 1: 51%, wave 2: 42%, wave 3: 66%, wave 4: 86%, P_{trend}: <0.001). Procedural success was also achieved more often over time with fewer complications and in-hospital adverse events.

At discharge, aggressiveness of medical therapy increased over time. Specifically, more patients were prescribed aspirin (wave 1: 94%, wave 2: 94%, wave 3: 95%, wave 4: 97%, P_{trend}: <0.001), ticlopidine or clopidogrel (wave 1: 67%, wave 2: 82%, wave 3: 94%, wave 4: 96%, P_{trend}: <0.001), beta-blockers (wave 1: 65%, wave 2: 71%, wave 3: 77%, wave 4: 81%, P_{trend}: <0.001), angiotensin converting enzyme (ACE) inhibitors(wave 1: 29%, wave 2: 34%, wave 3:

46%, wave 4: 56%, P_{trend}: <0.001) and lipid lowering medications (wave 1: 46%, wave 2: 60%, wave 3: 76%, wave 4: 87%, P_{trend}: <0.001). However, prescription of calcium channel blockers and long acting nitrates decreased from 36% and 33% respectively in wave 1 to 15% in wave 4 (P_{trend}:<0.001 for both).

2.4.1 Angina in the past 6 weeks at one – year of follow-up

When contacted at one year, fewer patients, over time, reported angina of any severity in the past 6 weeks – both in the overall cohort (24% in wave 1 to 20% in wave 4, P_{trend}: <0.001) and among symptomatic patients (Figure 2.1). Additionally, angina rates at 1-year were higher among patients who had undergone index PCI for stable angina, compared to other reasons. Among patients who reported angina at one year (Table 2.2), there was an indication of more frequent episodes of angina (i.e. 3 or more times per day) in the latter recruitment waves (P_{trend}: 0.01). While 1-year reported use of aspirin, beta-blockers, ACE inhibitors, lipid lowering medications and antiplatelet therapy increased over time, use of calcium channel blockers and long acting nitrates decreased (P_{trend} for all: <0.001), the need for repeat revascularization (both PCI and CABG), following index PCI, decreased significantly across the waves (Table 2.2).

2.4.2 Temporal trends in post-PCI angina within baseline characteristics

The overall decreasing trend in patient-reported angina rates over time was evident in most subgroups classified by patient and procedural characteristics (Table 2.3). However, there was evidence suggestive of interaction (differential effect) with PCI era for several characteristics. This included evidence of a large reduction in rates of angina over time for patients with prior

MI, diabetes, lack of initial procedural success, procedural use of anti-platelet agents and those discharged on ≥ 2 medication classes (beta blockers, long-acting nitrates, calcium-channel blockers, ACE-inhibitors). In contrast, difference in angina rates by history of prior PCI widened over time.

2.4.3 Risk of post-procedural angina:

Compared to wave 1, the unadjusted risk of follow-up angina was 4-28% lower for more recent waves, with statistical significance achieved for waves 3 and 4; adjustment for cohort differences did not alter the pattern (Figure 2.2). Secondary univariate analyses in only successful procedures (angiographic and procedural) or those in whom symptoms (stable or unstable angina or acute MI) were the primary reason for index PCI, showed similar trend. Of note, overall use of stents (vs no stent) was univariately associated with reduction in follow-up angina risk in all 4 waves (Relative risk in waves 1, 2, 3, 4: 0.77, 0.79, 0.63, 0.62, P≤ 0.05 for all).

Patients alive but missing angina information at follow-up were more often younger (65% vs 54%, P: 0.02) with multivessel disease (64% vs 59%, P: 0.34), had undergone procedures mostly for AMI (29% vs 24%, P: 0.88), with fewer calcified (51% vs 54%, P: 0.06) and more ostial lesions (15 % vs 10%, P: 0.06); procedural (93% vs 97%, P: 0.01) and total angiographic (88% vs 94%, P: <0.01) success was achieved less frequently. However, results of the sensitivity analysis were similar to that in the overall cohort (relative risk of angina for waves 2, 3, 4 with wave 1 as reference: 0.97, 0.81, 0.81; P ≤ 0.001 for waves 3 and 4).

2.4.4 Factors associated with follow-up angina in contemporary practice

Of the 1846 survivors in wave 4, 1596 had undergone index PCI for angina (stable /unstable) or AMI. Among the baseline independent predictors of 1-year angina, age > 65 years was associated with decreased risk and female gender, history of CHF, peripheral vascular disease and prior CABG/ PCI were associated with increased risk of follow-up angina (Table 2.4). Patients discharged on ticlopidine or clopidogrel were less likely to report angina at one year (RR: 0.74, P:0.06) whereas those hospitalized for MI or repeat PCI following the index procedure showed a 1.5-fold increase in risk of angina at 1-year.

Although overall stent use, which was near universal in wave 4, was not an independent predictor, it was univariately associated with reduced risk of post-PCI angina (relative risk (95% CI):0.623 (0.40-0.96)). However, when stents were used in this cohort of symptomatic patients (angina or acute MI), drug-eluting stents were associated with increased, albeit non-significant, unadjusted risk (relative risk (95% CI):1.16(0.89-1.50))

2.5 DISCUSSION

This report documents favorable temporal trends in patient-reported post-PCI angina in a prospective multicenter registry, spanning a decade of clinical practice. Specifically, prevalence and risk of post-procedural angina has decreased over time and parallels technological evolution and improved use of secondary pharmacotherapy in the field.

The NHLBI-sponsored Dynamic registry cohorts primarily represent evolution in PCI since its initial use [8], with routine and increasing use of stents (bare metal and coated),

antiplatelet regimen, and aggressive secondary CAD management. Indeed, this evolution has resulted a proven reduction in the need for repeat revascularizations, even in a heterogeneous patient (and lesion) population [24, 46, 47]. However, with the lack of demonstrable mortality benefit, the true value of PCI, especially from a patient's perspective, lies in symptom relief. Although numerous reports have demonstrated favorable impact of PCI on post-procedural symptoms [45, 26, 48;48, 49], their findings were from specific phases of PCI advancement. The current report is unique in that it is prospective, spans over a decade of real world clinical practice and reflects improvements in prevalence of post-PCI angina.

The association of PCI era with post-PCI angina could be attributed to a combined impact of new technology, adjunct therapy, and more aggressive secondary management. In the early stent era, Holubkov et al [45] showed that overall stent use was associated, although not independently, with fewer symptoms. Similarly, in the present report, stent use was univariately associated with reduced risk of follow-up angina, both overall and in individual cohorts. Additionally, in keeping with recommended guidelines [47], secondary management with aspirin, antiplatelets, and lipid-lowering medications is more frequently pursued. Even with the overall reduction in anti-anginal mediation use, we see an increase in beta-blocker use with a contrasting decrease in nitrates and calcium-channel blockers. Although information on baseline use or reason for follow-up use was not available in this registry, this is a likely reflection of the beneficial effects of beta-blockers on all-cause mortality and morbidity [50]. Interestingly, compared to wave 1, risk of angina was significantly reduced only for the two most recent waves. One possible explanation is a likely similarity between the first two waves with the latter cohorts witnessing more variety and use of technology (intracoronary radiation, atherectomy devices, drug-eluting stents) and post-procedural management, in a widened patient and

procedural profile. On other hand, PCI, over time, has been increasingly applied to sicker patients and our original analyses included only survivors with one year information. Risk estimates from sensitivity analyses, however, showed little variation.

Post-revascularization angina, in spite of reduced prevalence, remains a matter of concern, especially since PCI is aimed at targeting ischemia-causing 'culprit' lesions. Some important factors that may result in post-PCI symptoms include failed index procedure (restenosis or residual disease) or new or progressed disease. While technological advancements have dramatically reduced restenosis rates [12], residual multivessel or left main disease has been shown to be an independent predictor of follow-up angina [45]. Therefore, given the diverging trends in treatment strategy (fewer vessels attempted compared to number of vessels diseased) over time [24, 27], one might have expected an increase in angina rates over time. However, the observed reverse trend is encouraging and may be attributed to safer, more successful procedures followed by aggressive secondary management. Atherosclerosis is a chronic process and disease progression, though expected, cannot be adequately predicted, even in patients undergoing PCI[40]. This further underscores the need for continued aggressive risk factor modification. The latter may also influence outcomes in specific co morbid characteristics and to this end, the apparent substantial reduction in post-PCI angina among patients with diabetes deserves mention. This marked improvement lends support to the favorable trends seen in other in-hospital and one year outcomes observed in this subset [51].

2.5.1 Predictors of Angina in contemporary practice

Post-procedural evaluation, in real world practice, is more often triggered by symptoms and identifying significant predictors could, therefore, serve as a 'susceptibility' index. This is

especially important in contemporary practice, given concerns of cost-effectiveness of coated stents [52, 53]. Factors independently predictive of increased risk of follow-up angina, in the DES-era, were female sex, age < 65 years, prior revascularizations and intercurrent hospitalizations for MI or repeat PCI. In spite of the reported gender-specific improvement in in-hospital and long-term outcomes following PCI [54,55,56], female gender, also associated with under-use of evidence-based medications [57] , remains a significant risk factor for post-procedural symptoms [45, 58]. In an era of improved success and single-digit restenosis rates, patients with prior PCI and those requiring repeat PCI, may be representative of a unique subset of alleviated disease burden. The differential impact of these characteristics on post-PCI angina further supports this notion, and warrants closer attention. Additionally, in light of emerging reports of off-label use [16] and adverse events with drug-eluting stent use [59, 60], the increased risk of angina, though non-significant, in this cohort of symptomatic patients, needs further exploration.

The NHLBI-sponsored Dynamic registry relies on voluntary participation and majority of the clinical sites are moderate-large volume centers, limiting universal generalizability of the findings. Lack of information on baseline symptom profile limits ability to assess benefit from the initial procedure. Angina, the outcome of interest, is highly subjective and also influenced by psychosocial aspects [58,61]. Data on these and recommended lifestyle modifications were not routinely collected. Further analysis is underway to evaluate patient-reported quality of life, as means to validate self-reported symptom status, as well as temporal trends in supplemental therapy used to achieve it in this cohort.

2.6 CONCLUSION

Our report, from a large prospective, multicenter registry, documents favorable temporal trends in prevalence and risk of post-PCI angina in a decade of real world clinical practice. In spite of this overall trend, women and patients with prior or repeat PCI continue to remain at high-risk for post-procedural symptoms.

Table 2.1: Baseline patient, procedural and discharge characteristics of patients alive at 1 year following PCI in the NHLBI-sponsored 1997-2004 Dynamic Registry

	Dynamic Registry Waves			
	1	**2**	**3**	**4**
Total patients	**1793**	**1417**	**1379**	**1657**
Patient characteristics				
Age >65 years †	42.6	46.4	49.5	46.4
Female	31.2	30.6	32.7	28.2
White †	88	90.8	89.3	84.9
Prior CABG ‡	16	18.5	18.6	20.4
Prior MI ‡	38.5	31.4	26.1	26.7
Prior PCI *	29.6	29.1	32.3	32.1
Severe concomitant non-cardiac disease ‡	27.9	32	36.4	35.4
Cerebrovascular	5.2	6.4	5.6	7.9
Peripheral artery disease	7	6.4	8.2	8.4
Pulmonary disease	6.2	8.7	7.6	6.7
Cancer	6	6.4	8.1	7.3
Renal failure /Insufficiency	2.8	3.7	5.6	7.3
Other	7.9	10.3	15	13.9
History of Diabetes ‡	25.1	25.5	27	32.1
History of CHF	8.5	7.5	10.1	7.9
History of Hypertension ‡	58.8	62	71.8	76.5
Smoking †				

Table 2.1 continued

Never	31.9	30	34.5	38
Former	43.8	45.7	43.9	41.5
Current	24.3	24.3	21.6	20.5
Mean Ejection fraction § ‡	55.9	54.1	52.7	52.2
Baseline Vessel Disease ‡				
Single	42.8	44.4	38	34.4
Double	32	30.4	31.8	32.7
Triple	23.5	25.1	30.2	32.9
Graft body disease	11.4	12.8	13.2	14.7
Total occlusion (native vessels or graft)	35.5	34.1	35.5	38.9
Proximal LAD disease	32.7	35.9	32.5	35.5
Mean significant lesions †	2.8	2.9	3.1	3.1
Procedural data				
Primary reason for index PCI ‡				
Stable Angina	26.7	21.3	20.4	23.1
UA / AMI	64.2	71.5	70	63
ACAD /Others	9	7.2	9.7	13.9
Circumstances of index PCI ‡				
Elective	67.4	57.9	51.4	58
Urgent	23.3	32.3	38.1	31.3
Emergent	9.3	9.9	10.4	10.7
# of lesions attempted †				

Table 2.1 continued

One	67.3	69.2	69.5	72.1
≥ 2 or more	32.7	30.8	30.5	27.9
# of vessels attempted †				
1 native vessel only	83.1	82.6	82.2	79.2
2 -3 native vessels only	9.2	9.2	9.7	12.8
Graft +/- native vessels (s)	7.6	8	8.1	8
Complex lesions (evidence of thrombus, ostial , bifurcation, calcified, chronic total occlusions) ‡	61.6	59.6	53.9	53.9
Ulcerated	15.3	15.7	15.2	15
Proximal LAD attempted	17.3	18.6	15.6	15.5
Gp IIb/IIIa inhibitors 24 hrs prior /during PCI ‡	23	32.4	52.4	34.5
Ticlopidine/Clopidogrel < 24hrs/during PCI ‡	51	42.1	66.1	86.3
Device use				
Overall balloon use ‡	97.4	92	74.8	75.4
Overall stent use ‡	66.5	80.7	88.3	93.4
In-hospital outcome and discharge data				
Overall total angiographic success ‡	93	93.1	94.8	95.5
Procedure success *	96.8	97	97.7	97.6
Any in-hospital complication (dissection, side branch occlusion, abrupt closure, slow flow, embolization) ‡	18.9	9.5	7.3	7.6
MI (in-hospital)	2.6	2.9	1.9	2.4

Table 2.1 continued

CABG (in-hospital)	1.1	1.1	0.6	0.8
Major entry site complication †	2.7	3.8	2.9	4.7
Medications at discharge				
Aspirin ‡	94.2	93.6	95	96.9
Beta-blockers ‡	65.3	70.8	77	81.2
Long-acting nitrates ‡	33.4	27.3	24.8	15.4
ACE-Inhibitors ‡	28.6	34.3	45.9	55.7
Calcium channel blockers ‡	35.9	27.3	20.7	15.1
Lipid lowering medications ‡	45.5	60	76.1	87.2
Digitalis ‡	6.5	6.3	5	3.4
Diuretics ‡	14.1	17.8	20.7	23.4
Warfarin †	5.5	6.1	7.6	7.5
Low-molecular-weight heparin**	1.3	1.1	0.6	0.7
Ticlopidine /Clopidogrel ‡	67.1	81.5	94	96.1

P_{trend} using Cochran-Armitage test for dichotomous variables and JT test for continuous & ordinal variables: * ≤0.10, ** ≤ 0.05, † ≤ 0.01, ‡ ≤0.001; § 33% of data missing

ACE: Angiotensin-converting enzyme inhibitors, CHF: Congestive heart failure, CABG: coronary artery bypass grafting, LAD: Left anterior descending artery, MI: Myocardial infarction, PCI: Percutaneous coronary intervention

Table 2.2: Temporal trends in post-procedural angina and related characteristics at one year follow-up in the NHLBI-sponsored 1997-2004 Dynamic Registry

	Dynamic Registry Waves			
	1	**2**	**3**	**4**
	(1997-98)	**(1999)**	**(2001-2002)**	**(2004)**
Total Patients	**1793**	**1417**	**1379**	**1657**
Presence of Angina in past 6 weeks ‡	24.3	22.3	17.9	20
Severity of Angina (among those with angina)				
Stable CHC I/II Angina	54.5	54.2	59.5	58.6
Stable CHC III/IV Angina	20.5	20.8	23.2	12.9
Unstable Angina /AMI	25.1	25	17.3	28.5
Frequency of Angina (among those with angina) †				
3 or more times/day	4.3	7.7	6.3	9.6
1 to 2 times/day	13	10	13.5	13
Several times/week	30.9	31.4	38.8	31.2
Once/week or less	51.9	50.8	41.4	46.3
Angina Status and use of Long-acting nitrates ‡				
No Angina, No nitrates	59.5	65.1	69.4	71.2
No Angina, Nitrates used	15.7	11.7	11.9	8
Angina	24.3	22.4	17.8	20
Medication use in the past 6 weeks				
Aspirin ‡	85	84.9	84.9	89.9

Table 2.2 continued

Ticlopidine /Clopidogrel § ‡	1.7	3.8	16.9	59.8
Lipid lowering medications ‡	56.8	66.3	76.3	82.8
ACE-Inhibitors ‡	28.1	33.2	45.5	48.6
Beta-blockers ‡	60	65.4	70.3	75.5
Long-acting nitrates ‡	27.1	21.1	17.6	13.2
Calcium channel blockers ‡	29.8	24.6	21.3	16.4
Sublingual NTG ‡	76	67.4	63.8	61.3
Warfarin*	5.5	5.8	7.3	7.1
Angiotensin receptor blocker ‡	1.9	4.3	5.4	12.5
AHM ‡	7.7	6.8	8.9	10.6
Diuretics ‡	20.1	21.5	24.1	25.8
Digitalis ‡	7.2	6	5.5	4.1
Hospitalizations over 1 year				
Angina ‡	19.3	17.5	12.5	13.9
MI	5.2	5.4	4.8	4.5
Repeat PCI ‡	16	12.9	12.2	9.5
CABG ‡	6.9	6.2	4	2.5

P_{trend} using Cochran-Armitage test for dichotomous and JT test for ordinal variables:* ≤ 0.05, † ≤ 0.01, ‡ ≤ 0.001; § Information on 1-year Clopidogrel use not routinely collected in Waves 2 and 3; ACE: Angiotensin-converting enzyme inhibitors, NTG: Nitroglycerin, AHM: Vasodilators/other anti-hypertensive medications, MI: Myocardial infarction, PCI: Percutaneous coronary intervention, CABG: coronary artery bypass grafting

Table 2.3: Prevalence of one-year post-procedural angina within baseline and in-hospital characteristics in the NHLBI-sponsored 1997-2004 Dynamic Registry

	Overall		Waves of the Dynamic registry								P_{trend*}	P **
			1		2		3		4			
	Total (N=6246)	Angina (%)	Total (N=1793)	Angina (%)	Total (N=1337)	Angina (%)	Total (N=1377)	Angina (%)	Total (N=1641)	Angina (%)		
Age > 65 years												
Yes	2872	19.3	764	21.1	657	22.2	682	16.3	769	17.7	0.02	1
No	3374	23.2	1029	26.7	760	23	697	19.4	888	22.1	0.004	
Sex												
Male	4334	20.1	1233	22.7	983	21.6	928	16.5	1190	19	0.003	0.8
Female	1912	24.3	560	27.9	434	25.1	451	20.6	467	22.7	0.02	
Race												
White	5504	20.8	1578	24	1287	22.2	1232	16.5	1407	19.5	<0.001	0.36
Non-whites	742	26	215	26.5	125	27.2	147	28.6	246	23.2	0.45	
Prior MI												
Yes	1908	24.8	684	28.7	439	26.2	353	19.8	432	21.3	0.001	0.1
No	4237	19.8	1091	21.5	957	21	1000	17.1	1189	19.4	0.07	

Table 2.3 continued

Prior CABG												
Yes	1141	29	286	31.2	262	30.5	256	24.6	337	29.4	0.4	0.18
No	5099	19.7	1503	23.1	1155	20.9	1123	16.3	1318	17.6	<0.001	
Prior PCI												
Yes	1919	27.1	528	29.2	413	27.9	446	24.4	532	26.5	0.21	0.14
No	4317	18.8	1257	22.2	1004	20.5	933	14.7	1123	17	<0.001	
Severe Concomitant Non-Cardiac Disease												
Yes	2034	23	497	25	452	27.2	501	18.4	584	22.1	0.04	0.7
No	4185	20.5	1284	24	962	20.5	875	17.5	1064	18.9	0.001	
History of Diabetes												
Yes	1707	23.4	443	29.8	360	25	372	19.4	532	19.7	<0.001	0.03
No	4505	20.6	1321	22.6	1053	21.9	1007	17.3	1124	20.2	0.03	
History of CHF												
Yes	522	25.5	152	26.3	106	24.5	137	24.8	127	26	0.94	0.24
No	5625	21	1628	24.1	1305	22.5	1220	17.1	1472	19.4	<0.001	
History of Hypertension												
Yes	4151	22.5	1039	25.6	874	25.5	980	18.7	1258	20.7	<0.001	0.92
No	2034	19.1	728	22.4	524	17	382	16	385	17.7	0.02	

Table 2.3 continued

Smoking												
Never	1978	21.4	546	23.4	398	21.9	435	19.3	599	20.7	0.19	0.61
Ever (current + former)	3900	21.6	1168	24.8	929	23.1	826	17.8	977	19.5	<0.001	
Multivessel disease												
Yes	3742	22.8	1026	25.6	787	25	853	18.9	1076	21.6	0.03	0.68
No	2482	19.4	767	22.6	629	19.7	523	16.3	563	17.6	0.01	
Graft body disease												
Yes	812	30.4	205	31.2	181	34.3	182	26.9	244	29.5	0.41	0.34
No	5434	20	1588	23.4	1236	21	1197	16.5	1413	18.4	<0.001	
Any total occlusion												
Yes	2254	24.5	637	27.3	483	26.3	489	20.3	645	23.7	0.04	0.5
No	3992	19.6	1156	22.7	934	20.8	890	16.5	1012	17.7	0.001	
Proximal LAD disease												
Yes	2131	22.5	586	23.2	508	27.6	448	18.8	589	20.2	0.03	0.82
No	4115	20.8	1207	24.9	909	19.9	931	17.4	1068	19.9	0.001	
Reason for index PCI												
Stable Angina	1445	24.6	479	27.4	302	25.8	281	20.3	383	23.5	0.08	-
Unstable Angina / AMI	4172	22.1	1151	24.7	1013	23.3	964	18.6	1044	21.4	0.01	0.79
ACAD /Other	627	9.1	162	13	102	6.9	133	7.5	230	8.3	0.16	0.92

Table 2.3 continued

Procedural Circumstances												
Elective	3698	21.5	1208	24.8	820	22	709	17.9	961	19.6	0.001	-
Urgent	1918	21.9	417	24.7	457	23.6	526	19.6	518	20.5	0.05	0.40
Emergent	627	19.1	166	20.5	140	23.6	144	11.1	177	20.9	0.51	0.65
# Vessels attempted												
1	5104	20.9	1489	24.1	1170	21.9	1132	17.3	1313	19.4	<0.001	0.47
≥ 2 (native +/- graft)	1132	23.5	301	25.3	242	25.6	245	20.4	344	22.7	0.27	
# Lesions attempted												
1	4333	21.6	1205	25.6	937	22	957	18.4	1194	19.8	<0.001	0.25
≥ 2	1903	20.8	585	21.7	435	23.7	420	16.7	463	20.7	0.25	
Complex lesions attempted (bifurcation, calcification, ostial, chronic total occlusions)												
Yes	3516	20.8	1105	22.7	790	22.5	737	17.5	884	19.5	0.01	0.52
No	2632	22	688	26.9	547	21.9	640	18.3	757	20.6	0.002	
Proximal LAD attempted												
Yes	1044	19.2	310	17.4	262	26.3	215	15.8	257	16.7	0.33	0.56
No	5192	21.8	1480	25.7	1150	21.7	1162	18.2	1400	20.6	<0.001	
Any in-hospital complication (dissection, side branch occlusion, abrupt closure, slow flow, embolization)												
Yes	699	22.5	338	25.2	134	20.9	101	17.8	126	20.6	0.15	0.87
No	5547	21.2	1455	24.1	1283	22.8	1278	17.8	1537	20	<0.001	

Table 2.3 continued

Overall Balloon use												
Yes	5331	21.1	1742	24.3	1303	22.9	1031	15.8	1250	19.2	<0.001	0.2
No	915	23	46	26.1	114	20.2	348	23.9	407	22.6	0.92	
Overall Stent use												
Yes	5100	20	1192	22.6	1144	21.4	1217	17	1547	19.4	0.01	0.39
No	1146	27.4	601	27.8	273	27.8	162	24.1	110	29.1	0.79	
Procedural use of Gp IIb/IIIa Inhibitors												
Yes	2165	19.5	412	21.1	459	22.4	723	17.8	571	18	0.07	0.93
No	4081	22.4	1381	25.3	958	22.8	656	17.8	1086	21.1	0.002	
Procedural use of Ticlopidine / Clopidogrel												
Yes	3853	20.6	914	23	597	21.9	912	17.5	1430	20.4	0.07	0.05
No	2393	22.7	879	25.7	820	23.2	467	18.4	227	17.6	0.001	
Overall Angiographic Success												
None /Partial	370	24.9	126	28.6	98	27.6	71	18.3	75	21.3	0.12	0.51
Total	5866	21.1	1664	24	1314	22.2	1306	17.8	1582	20	0.001	
Procedure Success (partial or total angiographic success without Q-wave MI/Emergency CABG)												
Yes	6066	21.3	1733	24	1369	22.4	1346	17.8	1618	20.2	0.001	0.13
No	170	24.7	57	33.3	43	25.6	31	19.4	39	15.4	0.03	

Table 2.3 continued

Aspirin												
Yes	5928	21.1	1689	23.9	1325	22.2	1308	17.9	1606	20	0.001	0.25
No	315	25.7	104	30.8	91	29.7	69	15.9	51	21.6	0.05	
Ticlopidine / Clopidogrel												
Yes	5246	20.5	1203	22.7	1155	22.3	1296	17.7	1592	19.7	0.01	0.84
No	1000	26.2	590	27.6	262	24.1	83	20.5	65	29.2	0.46	
Lipid lowering medications												
Yes	4160	21.2	815	26	850	22.5	1050	18	1445	20	<0.001	0.64
No	2086	21.8	978	22.9	567	22.9	329	17.3	212	20.3	0.09	
# Discharge medications (beta blockers, calcium channel blockers, long-acting nitrates, ACE-inhibitors)												
0-1	2735	18.2	819	18.8	689	18.1	565	16.3	662	19.3	0.96	0.001
≥ 2	3508	23.8	974	29	727	27	812	18.8	995	20.5	<0.001	

*P value for test of trend in angina rates within each characteristic; ** P value for interaction term of characteristic with wave

Table 2.4: Predictors of one year post-PCI angina in contemporary practice

	Baseline factors only	P value	In-hospital factors and 1-yr outcomes added	P value
	Relative risk (95% CI)		Relative risk 95% CI	
Female (vs Male)	1.28 (1.06-1.55)	0.01	1.24 (1.04 - 1.48)	0.02
Whites (vs non-whites)	0.99 (0.79 - 1.25)	0.95	0.99 (0.80 - 1.23)	0.93
Age ≥ 65 years (vs < 65 yrs)	0.73 (0.60 - 0.89)	<0.01	0.77 (0.65 - 0.93)	0.01
History of congestive heart failure	1.27 (0.95 - 1.70)	0.1	1.25 (0.94 - 1.65)	0.12
Concomitant peripheral vascular disease	1.35 (1.02 - 1.80)	0.04	1.21 (0.92 - 1.59)	0.16
Prior bypass surgery	1.45 (1.17 - 1.78)	0.001	1.38 (1.13 - 1.69)	<0.01
Prior PCI	1.28 (1.05 - 1.54)	0.02	1.19 (1.00 - 1.43)	0.05
Index PCI for acute MI (vs stable or unstable angina)	0.71 (0.56 - 0.89)	<0.01	0.75 (0.61 - 0.92)	0.01
Discharged on antiplatelets	-	-	0.74 (0.49 - 1.02)	0.06
MI during 1-year follow-up	-	-	1.54 (1.13 - 2.12)	0.01
Repeat PCI during one-year follow-up	-	-	1.52 (1.21 - 1.90)	<0.001

Additional covariates considered but did not enter model: **Baseline factors:** concomitant cerebrovascular disease, history of hypercholesterolemia, significant graft body disease before index procedure, presence of native total occlusions; **In-hospital and one year outcomes:** use of

Table 2.4 continued

Gp IIb/IIIa inhibitors < 24 hours or during index procedure, Use of drug-eluting stents, overall use of balloons, discharge medications: long-acting nitrates, beta blockers, angiotensin-converting enzyme inhibitors and calcium channel blockers.

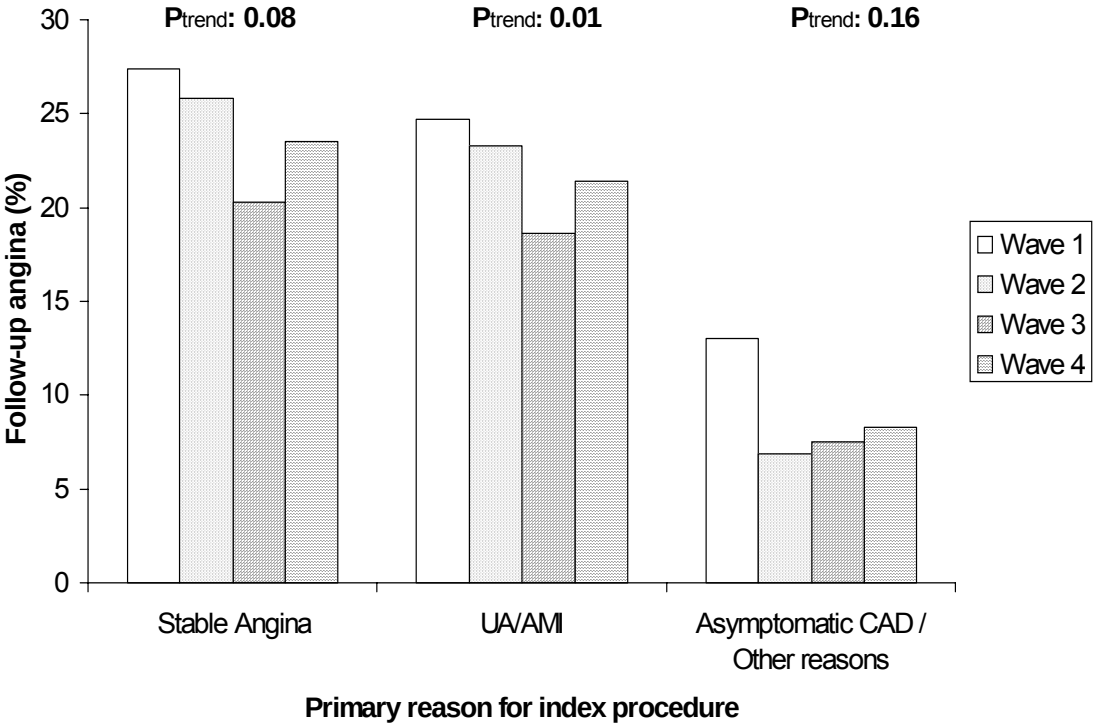

Figure 2.1: Prevalence of one-year post-procedural angina by primary reason for index PCI in the NHLBI-sponsored 1997-2004 Dynamic Registry

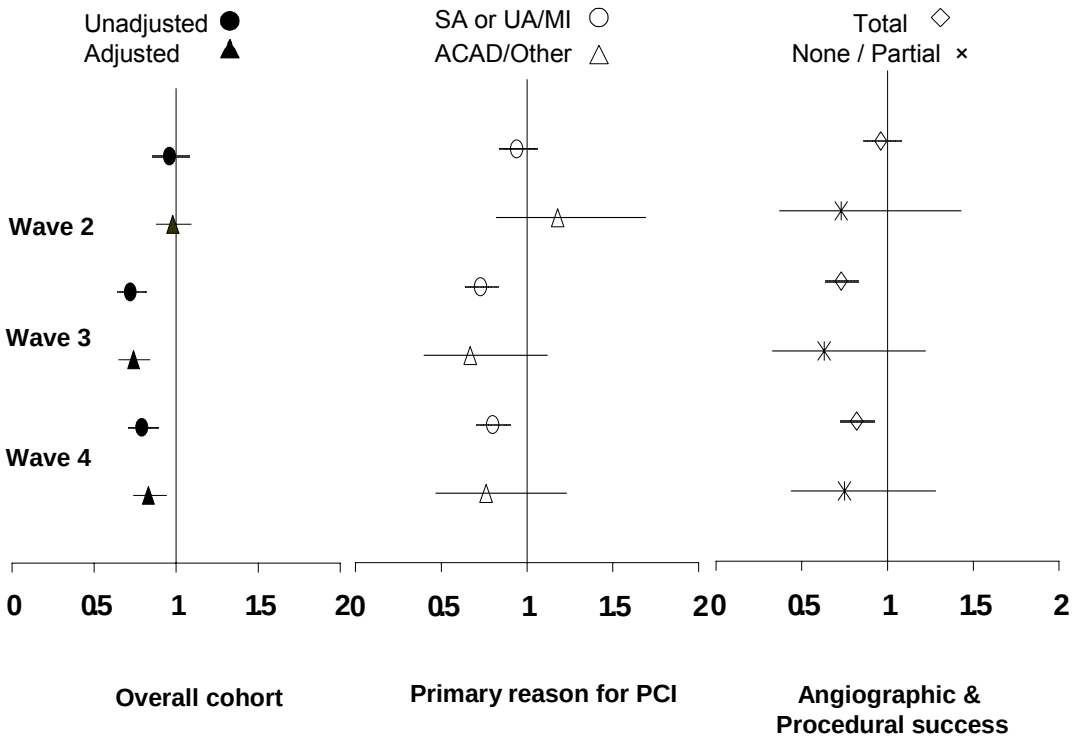

Figure 2.2: Relative risk of one year post-PCI angina in the overall cohort and in specific subsets in the NHLBI-sponsored 1997-2004 Dynamic Registry

Covariates in the final model for the overall cohort: Age ≥ 65 years, female gender, race, prior PCI, prior CABG, severe concomitant non-cardiac disease, history of hypertension, smoking status, primary reason for index PCI (stable or unstable angina, acute MI, other reasons), overall stent use, repeat PCI over one year, discharged on ≥2 of the following medications (beta-blockers, calcium-channel blockers, ACE-inhibitors, long-acting nitrates)

3.0 TEMPORAL TRENDS IN AGGRESSIVENESS OF SUPPLEMENTAL THERAPY FOLLOWING PERCUTANEOUS CORONARY INTERVENTION AND THE ASSOCIATED IMPACT ON QUALITY OF LIFE AT ONE YEAR FOLLOW-UP – A REPORT FROM THE NHLBI-SPONSORED DYNAMIC REGISTRY (1997-2004)

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3.1 ABSTRACT

Durability of symptom-relief, following percutaneous coronary intervention (PCI), has often been attributed to repeat revascularization. However, technological evolution in the field has resulted in dramatic reductions in rates of restenosis and repeat intervention. Our objective, therefore, is to document temporal trends in post-PCI supplemental therapy and evaluate its influence on quality of life (QOL), in 6246 consecutive patients in the NHLBI-sponsored 1997-2004 Dynamic registry. In the overall cohort, more patients reported use of pharmacological maintenance therapy (PMT, ≥1 of beta-blockers, calcium channel blockers and long-acting nitrates) both within and across the four waves (wave 1: 62%, wave 2: 64%, wave 3: 67%, wave 4: 72%, P_{trend} <0.001), with fewer repeat interventions. In every wave, more symptom-free patients, compared to symptomatic counterparts, reported use of no additional therapy (wave 1: 19 vs 11 %, wave 2: 20 vs 12%, wave 3: 19 vs 14 %, wave 4: 17 vs 15 %, $P < 0.05$ for all). QOL scores were higher with better physical activity and health status ratings in asymptomatic patients. On average, adjusted QOL scores improved significantly over time (mean scores – 6.2, 6.5, 6.6 and 6.6 for waves 1,2,3,4; P_{trend}: 0.01), but more importantly, differed by aggressiveness of therapy (mean scores – none: 6.6, MT: 6.5, repeat PCI: 6.0 and bypass surgery ± PCI: 6.3; P_{trend}: 0.03). Use of PMT, following initial PCI, has increased over time, with concomitant reduction in repeat interventions. Patient-reported QOL is influenced by nature of supplemental therapy and warrants consideration in post-PCI management.

3.2 BACKGROUND

Durability of symptom-relief with percutaneous coronary intervention (PCI), either alone or when compared to bypass surgery, is often attributed to subsequent repeat interventions and reliance on anti-anginal medications [26, 62]. Restenosis, necessitating repeat PCI, has also been shown to negatively impact patient's quality of life (QOL) following index procedure [63]. In the last few decades, however, the field of PCI has witnessed an explosion of new devices and improved adjunct therapy. Consequently, contemporary procedures, performed in heterogeneous population, are safer but more importantly, have resulted in a drastic reduction in restenosis and repeat interventions [24,27,43]. Additionally, in Paper 2 of this dissertation, favorable temporal trends were seen in patient-perceived symptoms, following initial PCI. Nevertheless, the related impact on the 'price' for achieving symptom-free status and its bearing on QOL remains to be explored.

The objectives of this analysis, therefore, are to 1) document temporal trends in aggressiveness of post-procedural therapy over one year, within anginal status, and 2) evaluate its influence on QOL indicators, in consecutive patients undergoing PCI in the NHLBI-sponsored 1997-2004 Dynamic registry.

3.3 METHODS

3.3.1 The NHLBI-sponsored 1997-2004 Dynamic Registry

Consecutive patients undergoing PCI were sequentially enrolled in recruitment waves: Wave 1: 1997-98, Wave 2: 1999, Wave 3: 2001-2002, and Wave 4: 2004; each cohort was enriched (oversampled) with women and minorities [24,44]. Baseline information on patient and procedural characteristics were ascertained by research coordinators trained in data collection. Written informed consent was obtained from participants at baseline for enrollment and follow-up contacts. The study protocol was approved by the Institutional Review Board of the University of Pittsburgh and those of all sites involved.

Patients were contacted by telephone, mail or during clinic visits, at one year of follow-up and information on angina and medication use, in past 6 weeks, physical activity (sedentary, mild, moderate, or strenuous), health status (poor, fair, good, very good and excellent), and QOL (11-point scale anchored between zero (dead or worse than being dead) and 10 (best)) were obtained. Hospitalizations for angina, myocardial infarction (MI), bypass surgery (CABG), and repeat PCI over one year were also recorded. Repeat PCI data included any procedure performed during a subsequent hospitalization after the index procedure. CABG included both in-hospital and post procedure events. Aggressiveness of supplemental therapy, following index PCI, was classified as follows: none (or only sublingual nitroglycerin as needed), pharmacological maintenance therapy (PMT, ≥1 of beta-blockers, calcium channel blockers and long-acting nitrates), repeat PCI, and CABG +/- repeat PCI.

Of the 8788 patients enrolled in the registry, ~ 90% consented for follow-up. At one year, 6246 consecutive patients provided angina information and constitute the analysis sample in this report.

3.3.2 Statistical analyses

Prevalence of symptom-free status, physical activity and health status at follow-up and aggressiveness of therapy are summarized as percentages and quality of life scores are summarized as mean (SD). Temporal trend in aggressiveness of therapy across the waves was assessed using the Jonckeheere-Terpsta test. Patient-reported outcomes of physical activity, health status and QOL scores were compared over time, by anginal status and in each level of aggressiveness of therapy. Difference in physical activity and health status (dichotomized as Poor / Fair vs Good/Very Good/Excellent) by anginal status was compared using the Cochran-Armitage or Chi-square tests, as appropriate. Difference in QOL scores by anginal status, in each wave, and trends over time was assessed using linear regression (PROC GLM in SAS); adjusted mean scores across waves were obtained from multivariate models that included age, gender, race and concomitant comorbidities (history of diabetes, hypercholesterolemia, hypertension, congestive heart failure, severe non-cardiovascular diseases). All analyses were performed with SAS version 9.1 (SAS Institute Inc, NC).

3.4 RESULTS

Of the 6246 patient alive and providing angina formation at one year, ~80% reported being angina-free (wave 1: 76%, wave 2: 77%, wave 3: 82%, wave 4:80%; P_{trend}: <0.001). Significant temporal trends were observed in the need and type of additional therapy, both in the overall cohort (P_{trend}: <0.001) as well as by anginal status (P_{trend} in those with angina: 0.02, P_{trend} for angina-free patients: 0.001) (Table 3.1). PMT was the predominant type of additional therapy both within and across the four waves (wave 1: 62%, wave 2: 64%, wave 3: 67%, wave 4: 72%). Comparison between angina-free and symptomatic patients revealed important differences. In every wave, more symptom-free patients reported no additional therapy, compared to symptomatic counterparts (wave 1: 19 vs 11 %, wave 2: 20 vs 12%, wave 3: 19 vs 14 %, wave 4: 17 vs 15 %). However, when supplementary treatment was required, angina-free status was achieved more often with maintenance therapy and fewer repeat interventions (more CABG and fewer repeat PCI in asymptomatic patients, compared to symptomatic counterparts). Trends in individual drug classes, used as maintenance therapy, showed that while fewer patients initially discharged on calcium channel blockers and long-acting nitrates, reported use at follow-up, use of beta-blockers increased across the waves (Table 3.2).

3.4.1 Quality of life following index PCI

Of the 5987 consecutive patients with QOL scores, mean QOL was significantly better in angina-free patients when compared to those reporting symptoms (mean(SD) score:7.3(1.9) vs 5.9 (2.1), P<0.001) at 1 year; among those with angina, QOL decreased as severity increased (mean (SD) score by CHC class: I: 6.4(1.9), II: 6.1(2), III:5.4(2.2), IV: 5.6(2.1), P_{trend}: <0.001).

Profile of follow-up physical activity, in each wave, was better in angina-free patients than their symptomatic counterparts (sedentary: 8 vs 15%, mild: 38 vs 48%, moderate: 46 vs 33%, strenuous: 8 vs 4%, P_{trend}: <0.001).

Over time, mean QOL scores significant improved in the overall cohort and in both symptom strata (mean (SD) scores – Angina: wave 1: 5.8 (2), wave 2: 5.8(2), wave 3: 5.9(2), wave 4: 6.2(2), P_{trend}: 0.01; No Angina: wave 1: 7.1 (2), wave 2: 7.4(2), wave 3: 7.4(1.9), wave 4: 7.3(1.9), P_{trend}: 0.01). Adjustment for potential confounders did not alter the pattern in the overall cohort (Table 3.3).

3.4.2 QOL and aggressiveness of supplemental therapy following index PCI

In general, patient-reported QOL indicators (QOL scores, physical activity, health status) varied by aggressiveness of additional therapy (Table 3.3). When analyzed within therapy subsets, mean QOL scores (unadjusted and adjusted) increased over time, albeit with varying statistical significance (Table 3.4). However, more patients in the 'no therapy' subset, in the recent waves, reported poor health status (wave 1: 4 %, wave 2: 5%, wave 3: 6% wave 4: 8%, P_{trend}: 0.02). Exploratory analysis in the small subset (N= 167) of symptomatic patients with no additional therapy showed trend towards increasing age with significantly more concomitant non-cardiac disease and history of prior revascularizations over time. Although procedural success did not differ across the waves, fewer lesions were attempted in setting of greater baseline disease burden (Table 3.5).

3.5 DISCUSSION

The NHLBI-sponsored Dynamic registry was primarily initiated to provide a snapshot of PCI with focus on patient and lesion profile, improvements in technology and the associated impact on clinical outcomes. Our report extends this to document temporal trends in supplementary therapy, following index PCI and its effect on patient-reported quality of life at one year.

Since its initial use in 1977 [8], PCI has seen rapid advancements resulting in high success rates, improved safety and reduced need for repeat interventions [18,43]. Previous studies have also reported favorable impact on post-procedural symptoms [31,45,49], albeit the lack of demonstrable mortality benefit. Few, however, explored the need and nature of post-procedural treatment in achieving symptom-free status or the associated impact on patient's quality of life. In the pre-stent era, ~ 1 in four patients, who underwent PCI outside of acute MI setting and were angina-free at one year, required repeat intervention (6% CABG and 19% repeat PCI) [4]. Subsequent analysis of symptomatic patients in the NHLBI-sponsored Dynamic registry showed lower rates repeat revascularization with increased use of maintenance therapy at one year [45]. This trend, as observed in our report, has continued over time - not only is symptom-free status achieved more often with pharmacological management, but more so in the setting of fewer repeat interventions. Coronary revascularization is an ideal opportunity for implementing evidence-based guidelines of post-procedural management and to this end, favorable temporal trends have been demonstrated in Paper 2 of this dissertation. Additionally, as seen in this report, more patients, when discharged on these medications, report use in the recent waves, suggestive of improved compliance. Early studies of PCI have often viewed reliance on anti-anginal therapy as a disadvantage of the procedure and admittedly, baseline use or reasons for discharge prescription were not collected in our registry. Nevertheless, improved understanding of

atherosclerosis, over the past few decades, has allowed for more effective use of cardiac medications, including beta blockers, in preventing recurrent events [64, 65, 66, 67]. Given the reduced need for long-acting nitrates over time, we speculate that beta blocker use, along with those of other recommended medications, probably reflects effective secondary prevention.

Patient's perspective of effectiveness of a treatment modality largely differs from clinical success. Patient-centered outcomes, including symptoms and quality of life, therefore, are gaining attention, both as part of decision-making as well as assessment of procedural performance [68,69]. Coronary artery disease, per se, imposes a considerable burden of illness and baseline symptoms significantly affect quality of life, even after percutaneous treatment [70]. Serial measurements of post-procedural health status (anginal frequency, QOL scores and physical function) showed that the greater improvement following CABG, compared to PCI, was primarily driven by restenosis in the latter group [63]. Our report extends this to show varying influence of specific type of additional therapy on QOL indicators, even in the absence of symptoms. Although treatment-specific QOL scores improved over time, there was considerable variation by aggressiveness of therapy. Clearly, this speaks to the multi-dimensional nature of QOL, which is not solely determined by symptoms, and therefore, must be considered during long-term evaluation.

The trend seen in poor health status when not on any additional therapy was mainly driven by symptomatic patients. Though small in number, the profile of symptomatic patients reflected an aging cohort, with prior revascularization and concomitant comorbidities, who may no longer be suitable for repeat interventions. On the other hand, lack of continued access to health-care facilities, especially among those with symptoms, cannot be ruled out. In a study of 480 patients, undergoing revascularization, affordability of health care was directly associated

with post-procedural recovery, especially among PCI patients [71]. Then again, health status in this report was assessed at a single time point and extended follow-up may have captured additional therapy.

The QOL benefits of PCI, alone or in comparison to other treatment modalities, are seen to vary in its various dimensions when captured using generic and disease-specific questionnaires [72,73,74,75]. The choice of instrument, however, is largely influenced by availability of resources, more so in registries that rely on voluntary participation. Information on patient-reported outcomes in our registry, though not extensive, was captured using brief questions from validated instruments [76], well-suited for telephone-based interviews. Further proof of validity, in this cohort, comes from the inverse relationship seen with worsening symptoms. Indeed, even with this limited information, our report demonstrates overall improvement in patient-reported indicators following PCI. In addition to being subjective with the potential recall bias, QOL is also influenced by social environment, relationships, personal values and emotions, details not collected in our registry. Furthermore, lack of baseline and serial measurements limits our ability to document magnitude and durability of improvement, both within individuals as well as between waves.

3.6 CONCLUSION

Angina-free status in one-year survivors of PCI is increasingly achieved with pharmacological therapy with fewer repeat revascularizations. Patient-reported quality of life is influenced by aggressiveness of therapy, following initial procedure and warrants consideration in post-procedural management.

Table 3.1: Temporal trends in supplemental therapy, following index PCI, in the NHLBI-sponsored 1997-2004 Dynamic Registry

		Dynamic Registry				
		Wave 1	**Wave 2**	**Wave 3**	**Wave 4**	**P_{trend}**
Entire cohort (N,%)		(N=1793)	(N=1417)	(N=1379)	(N=1657)	
None	(1090,17.5)	17.3	18.3	17.8	16.7	<0.001
PMT*	(4126,66.1)	61.6	64.3	66.9	71.7	
Repeat PCI	(722,11.6)	14.2	11.2	11.3	9.2	
CABG +/- Repeat PCI	(308,4.9)	6.9	6.2	4	2.5	
Patients with angina		(N=436)	(N=321)	(N=246)	(N=332)	
None		10.8	11.5	14.2	14.5	0.02
PMT*		64.2	64.8	65	65.7	
Repeat PCI		19.7	18.4	16.7	18.1	
CABG +/- Repeat PCI		5.3	5.3	4.1	1.8	
Patients with no angina		(N=1357)	(N=1096)	(N=1133)	(N=1325)	
None		19.4	20.3	18.5	17.2	0.001
PMT*		60.7	64.1	67.3	73.2	
Repeat PCI		12.5	9.1	10.2	6.9	
CABG +/- Repeat PCI		7.4	6.5	4	2.6	
Difference between anginal status (p value)		0.01	0.001	0.02	0.001	

* PMT: Pharmacological maintenance therapy (≥1 of beta-blockers, calcium channel blockers and long-acting nitrates)

Table 3.2: One year use of evidence based-medications among those prescribed at discharge in the NHLBI-sponsored 1997-2004 Dynamic Registry

	% use at follow-up				
	Wave 1	**Wave 2**	**Wave 3**	**Wave 4**	**P_{trend}**
Aspirin	86.8	87.6	86.6	90.9	0.001
Lipid lowering medications	80.1	83.5	84.7	86.8	<0.001
Antiplatelets**	2.0	4.5	17.1	60.6	<0.001
ACE-Inhibitors	65.4	67.5	69.9	70.8	0.03
Beta blockers	78.8	81.1	81.8	84.6	<0.001
Long-acting nitrates	54.9	43.5	44.4	48.8	0.02
Calcium channel blockers	61.4	64.5	60.7	59.6	0.58

** Information on follow-up use of clopidogrel not routinely collected in waves 2 and 3

Table 3.3: One-year quality of life indicators by aggressiveness of therapy in the NHLBI-sponsored 1997-2004 Dynamic Registry

	None (N=1031)	PMT (N=3983)	Repeat PCI (N=677)	CABG +/- PCI (N=296)	P_{trend}
QOL ratings (mean)					
Unadjusted	7.2	7	6.6	6.9	0.05
Adjusted*	6.6	6.5	6.0	6.3	0.03
Health status (%)					<0.001
Poor / Fair	25	28	35	29	
Good/Very Good/Excellent	75	72	65	71	
Physical Activity					<0.001
Sedentary	11	9	11	10	
Mild	34	41	44	39	
Moderate	45	43	40	43	
Strenuous	11	7	6	9	

*Adjusted for age, gender, race, and concomitant comorbidities (history of diabetes, hypercholesterolemia, hypertension, congestive heart failure, severe non-cardiovascular diseases)

Table 3.4: Temporal trends in quality of life and health status by aggressiveness of therapy in the NHLBI-sponsored 1997-2004 Dynamic Registry

	Wave 1	Wave 2	Wave 3	Wave 4	P_{trend*}
Overall					
QOL ratings					
Unadjusted	6.8	7	7.1	7.1	<0.001
Adjusted †	6.2	6.5	6.6	6.6	<0.001
% Poor / Fair health status	27	31	27	29	0.35
Aggressiveness of additional therapy					
None +/- Sublingual NTG					
QOL ratings					
Unadjusted	7.1	7.5	7.2	7	0.33
Adjusted†	6.4	6.9	6.7	6.4	0.65
% Poor / Fair health status, Overall	20	23	24	34	<0.001
Patients with angina	36	46	46	54	0.09
Patients with no angina	17	19	20	30	0.001
PMT‡					
QOL ratings					
Unadjusted	6.8	7.0	7.2	7.2	<0.001
Adjusted†	6.2	6.4	6.6	6.6	<0.001
% Poor / Fair health status, Overall	27	32	27	27	0.56
Patients with angina	48	56	49	49	0.96
Patients with no angina	20	24	22	22	0.46

Table 3.4 continued

Repeat PCI					
QOL ratings					
Unadjusted	6.3	6.4	6.7	6.9	0.01
Adjusted†	5.8	5.9	6.2	6.4	0.01
% Poor / Fair health status, Overall	33	38	33	38	0.38
Patients with angina	55	61	44	52	0.43
Patients with no angina	21	25	30	29	0.08
CABG +/- Repeat PCI					
QOL ratings					
Unadjusted	6.9	6.8	6.7	7.2	0.47
Adjusted†	6.4	6.3	6.3	6.7	0.45
% Poor / Fair health status, Overall	31	28	29	24	0.42
Patients with angina	57	41	50	33	0.35
Patients with no angina	26	25	24	23	0.73

* Test for trend: QOL scores – Linear contrast in general linear models, Health status – Cochran-Armitage test; †Adjusted for age, gender, race, and concomitant comorbidities (history of diabetes, hypercholesterolemia, hypertension, congestive heart failure, severe non-cardiovascular diseases) ‡ PMT: Pharmacological maintenance therapy (≥1 of beta-blockers, calcium channel blockers and long-acting nitrates)

Table 3.5: Profile of symptomatic patients with no additional therapy over one year in the NHLBI-sponsored 1997-2004 Dynamic Registry

	Dynamic Registry waves				
	1	2	3	4	
	(N=47)	(N=37)	(N=35)	(N=48)	P_{trend}
Age > 65 years	34	37.8	54.3	45.8	0.13
Female	29.8	21.6	40	25	0.98
White	89.4	94.6	80	85.4	0.28
Mean ejection fraction	55.2	49.5	52.7	52.4	0.67
Prior CABG	10.6	16.2	20	18.8	0.25
Prior PCI	27.7	24.3	42.9	41.7	0.06
Prior MI	36.2	27.8	14.7	25.5	0.15
Severe concomitant non-cardiac disease	31.9	18.9	54.3	47.9	0.02
Cerebrovascular	6.4	2.7	8.6	8.3	
Peripheral artery disease	4.3	0	2.9	16.7	
Pulmonary Disease	12.8	2.7	11.4	20.8	
Cancer	4.3	2.7	17.1	4.2	
Renal Failure/Insufficiency	0	2.7	0	8.3	
Other	6.4	8.1	25.7	12.5	
History of Diabetes	21.7	27	28.6	25	0.70
History of Congestive heart failure	8.7	5.4	20	10.9	0.38
History of Hypertension	60	59.5	68.6	75	0.09

Table 3.5 continued

Primary Reason for index PCI					0.56
Asymptomatic / Other	4.3	5.4	11.4	6.3	
Stable Angina	27.7	24.3	11.4	39.6	
Unstable Angina	46.8	40.5	62.9	29.2	
Acute MI	21.3	29.7	14.3	25	
Baseline disease status					0.01
Single vessel	63.8	62.2	34.3	41.7	
Double vessel	23.4	13.5	37.1	35.4	
Triple vessel	10.6	24.3	28.6	22.9	
Circumstances of Procedure					0.27
Elective	63.8	40.5	40	52.1	
Urgent	25.5	48.6	51.4	33.3	
Emergent	10.6	10.8	8.6	14.6	
≥2 Lesions attempted	25.5	29.7	17.1	20.8	0.38
Number of Vessels Attempted					0.04
1 native vessel only	93.6	91.9	82.9	81.3	
2 -3 native vessels only	4.3	0	5.7	10.4	
Graft +/- native vessels (s)	2.1	8.1	11.4	8.3	
Complex lesions attempted	66	70.3	54.3	43.8	0.01
Device Use					0.57
Balloon only or with drug	12.8	13.5	5.7	4.2	
Balloon & stent/stent only	61.7	64.9	77.1	75	

Table 3.5 continued

Balloon & stent & RA	10.6	10.8	2.9	2.1	
RA only/balloon & RA	12.8	5.4	0	0	
Other device	2.1	2.7	14.3	16.7	
In-hospital outcomes					
Procedural complications	19.1	10.8	2.9	4.2	0.01
Angiographic Success (partial or total)	97.9	94.6	100	97.9	0.34
Procedural Success	97.9	91.9	100	97.9	0.56
Anti-anginal medications at discharge					
Beta blockers	44.7	59.5	51.4	54.2	0.49
Long acting nitrates	31.9	13.5	14.3	12.5	0.02
Calcium channel blockers	27.7	10.8	14.3	8.3	0.02
Medications at follow-up					
Aspirin	76.6	64.9	77.1	85.4	0.18
ACE inhibitors	34	35.1	40	54.2	0.40
Angiotensin receptor blockers	0	2.7	14.3	16.7	0.001
Vasodilators / other anti-hypertensive medications	8.5	8.1	2.9	10.4	0.91
Diuretics	14.9	21.6	11.4	16.7	0.92
Digitalis	6.4	8.1	0	2.1	0.14
Lipid lowering medications	38.3	59.5	82.9	89.6	0.002

GENERAL DISCUSSION

SUMMARY OF FINDINGS

This dissertation, designed as three research papers, was primarily aimed at capturing the evolution of PCI and the associated impact on clinical and patient-reported outcomes, in prospective multicenter registries of real world clinical practice.

In Paper 1 , temporal trends in patient, lesion, and procedural characteristics were evaluated and in-hospital and one year outcomes were compared between the NHLBI-sponsored 1985-86 PTCA registry (era of balloon angioplasty) and 1997-2004 Dynamic registry (era of stents, brachytherapy and drug-eluting stents) cohorts. Results of this analysis revealed the heterogeneity in patients (and lesions) undergoing PCI, since its initial use [8], as well as the selective revascularization strategy in setting of greater baseline disease burden. Between 1985-86 and 2004, a wide variety of devices – balloons, bare metal stents, brachytherapy and more recently, drug-eluting stents – have been used. Use of dual antiplatelet therapy (aspirin and ticlopidine /clopidogrel) and other medications with evidence-based rationale have increased over time. Clinical performance, as characterized by procedural success and complications, dramatically improved with improved effectiveness (reduced need for repeat procedures) at one year. Even so, very little impact was observed in post-procedural mortality.

In Paper 2, prevalence of one-year angina was evaluated across the four waves of the Dynamic registry, representing the advent (wave 1) and uniform use (wave 2) of bare metal stents, intra-coronary radiation (wave 3) and advent of drug-eluting stents (wave 4); significant predictors in contemporary practice were identified. This analysis, from a large prospective, multicenter registry, documented favorable temporal trends with reduced prevalence and risk of post-PCI angina in a decade of real world clinical practice. Use of evidence-based secondary pharmacological therapy also improved over time. Differential impact of PCI era on post-procedural angina was observed in patients with these specific characteristics – diabetes, prior MI and prior revascularization. In contemporary practice, even with the improved secondary management, women and patients with prior or repeat PCI remain at high-risk for post-procedural symptoms.

In Paper 3, temporal trends in supplemental therapy following index procedure, specifically to achieve symptom-free status, were explored and the associated impact on quality of life indicators evaluated. In keeping with the evolution seen in the field, there was an observed shift towards greater use of maintenance therapy (more beta blocker use with fewer reports of nitrate and calcium channel blocker use) with concomitant reduction in rates of CABG and repeat PCI, in angina-free patients. Although patient-reported quality of life, significantly different by symptom status, improved over time, it was seen to vary by need and aggressiveness of supplemental therapy.

The above findings, from multicenter registries spanning two decades, together with those from previous reports [77, 27, 22, 78], speak to the dynamic nature of PCI. This transformation is indeed dramatic for a field initially considered in either single discrete lesions that did not warrant invasive surgeries or in sick patients in whom surgery was contraindicated or had to be deferred.

Clinical outcomes

For a long period of time, percutaneous treatment with balloon angioplasty and then bare-metal stents was plagued with abrupt vessel closures and restenosis, necessitating repeat procedures. This then became the driving force for the majority of innovations and improvisations in the field. It is, therefore, encouraging to see the dramatic reduction in procedural complications and rates of late repeat procedures, be it PCI or CABG, following the index procedure. On the other hand, the observed increase in early repeat PCI rates, which were small to begin with, are probably representative of a shift in preference for this technique, as opposed to early triage to CABG seen in initial cohorts.

In the last thirty years, the field has indeed come a long way with high procedural success and improved effectiveness (reduced repeat procedures). However, although rates of myocardial infarction (in-hospital and one year) have reduced over time, lack of demonstrable overall mortality benefit is intriguing. Detailed exploration of trends in outcomes by specific characteristics was beyond the scope of this dissertation. Nevertheless, previous publications from these registries have identified some subsets that may be responsible for this trend. Comparison of one year outcomes between patients undergoing PCI for stable versus unstable

angina showed little change in mortality rates in the latter cohort over the past 16 years [79]. In another report of 2,839 patients with complex lesions (defined as a lesion showing evidence of thrombus, calcification, bifurcation or ostial location, or chronic occlusion), both in-hospital and one year mortality rates were higher, compared to attempts on simple lesions [30].

Patient-reported outcomes

The focus of Papers 2 and 3 was temporal trends and impact of the aggressiveness of medical therapy on patient-reported outcomes among one-year survivors of PCI. Post-procedural symptoms and quality of life (QOL) indicators, evaluated during follow-up, were secondary outcomes of interest in the NHLBI-sponsored registries that relied on voluntary participation of clinical sites. As a result, brief questions, reliable and well suited for telephone based interviews, as opposed to extensive multidimensional questionnaires, were used for data collection. To the best of our knowledge, this is the first report to document favorable temporal trends in these outcomes and also, delineate the varying impact of aggressiveness of supplemental therapy in real world practice.

Analysis of patient-perceived outcomes is fitting given that, outside of acute settings, relief of symptoms to improve QOL is the underlying goal of revascularization. To this end, it is encouraging to see that the overall prevalence and risk of one-year angina has decreased over time, paralleling technological evolution and improved use of secondary pharmacotherapy in the field. Interestingly, specific characteristics were seen have a differential impact on 1-year angina. Presence of diabetes was associated with marked reduction in post-PCI angina over time, thus mirroring favorable trends in other in-hospital and one year outcomes in this subset [51]. Patients with prior PCI, on the other hand, were seen to have an increased risk, warranting closer

attention. Follow-up angina, of any prevalence, is concerning, more so, when observed in an era of improved procedural performance and aggressive secondary management. Given that the reported predictors were identified in symptomatic patients (reason for index PCI is stable or unstable angina or acute MI), these characteristics could well be representative of high ischemic burden. On the other hand, although recruitment in Wave 4 coincided with the early phase of first-generation DES use, off-label use cannot be ruled out. The overall increased (statistically non-significant) risk seen with DES use could, therefore, be associated fallout. The ongoing debate regarding inappropriate use of PCI in chronic stable angina, that could be medically managed, highlights another possible issue [80].

Comparability of benefits between revascularization techniques has often been attributed to additional procedures and reliance on anti-anginal medications in the PCI arm. This analysis, consistent with other studies, has demonstrated a reduction in need for repeat interventions following PCI. Furthermore, temporal trends in one-year asymptomatic status have been favorable with concomitant reduction in prescription and use of long-acting nitrates. With this as the background, Paper 3 was aimed at revisiting the need and aggressiveness of additional therapy following index PCI. Indeed, not only is asymptomatic status achieved more often today, but it is also achieved with more pharmacological therapy while fewer repeat interventions. Ideally, post-procedural management takes into consideration symptoms and functional limitations, in addition to objective evidence of ischemia. However, patient-centered outcomes have for long been considered too soft an endpoint to be incorporated in clinical practice. Patient's perspective of disease burden also differs considerably from that of the clinician [81, 82]. With the recent goals set forth by the Institute of Medicine [68], this is expected to change. The

present finding that patient-reported QOL scores are influenced by the type of additional intervention further underscores the importance of incorporating these measures.

ROLE OF REGISTRIES IN CONTEMPORARY PRACTICE

Healthcare practice and clinical guidelines have relied on randomized clinical trials (RCT) for evidence regarding treatment strategies. However, registries, in spite of some inherent biases, have held a prominent place in evaluation of real world clinical practice [83,24, 27,84,42].

Registries have been credited with highlighting widespread use of angioplasty [85] and subsequently prompting trials that compared it to other treatment options [86, 87]. More recently, DES-related thrombosis [42] was first identified using registry data, with no prior evidence in early trials [12,13]. Furthermore, characteristics identified as predictors (premature antiplatelet discontinuation, comorbidities like renal failure, diabetes, and low ejection fraction) are not often encountered in the controlled conditions of RCTs. This is because trials are designed to answer specific questions and the participants are carefully chosen, with inclusion / exclusion criteria, to ensure homogeneity between the different arms to optimize responsiveness. Registries, in contrast, are population-based with an aim to mirror 'real world' practice. Therefore, while RCTs are designed for proving efficacy of treatments, registries help with the timely evaluation of safety and effectiveness. With emerging concerns of mortality and stent thrombosis risk with DES use, and the Food and Drug Administration mandating extended postmarket surveillance, the role of registries in clinical research, though often underappreciated, is gaining prominence.

PUBLIC HEALTH SIGNIFICANCE

The burden of CAD is quite immense with an estimated 950,000 deaths each year and an approximate $368.4 billion in associated heath care costs [1]. PCI, as a treatment modality, has gained rapid acceptance resulting in a 300% increase in the number of procedures in the past two decades. Specifically, stent implantation has doubled [88] and 90% of these stents in the U.S are DES [89]. Any treatment modality, when applied in this magnitude, warrants frequent and timely monitoring of effectiveness and safety, a case in point being the latest controversy with DES use.

In the last few decades, there has also been much improvement in our understanding of atherosclerotic process. As a result, the observed decline in cardiovascular death rates since 1968 [90] has been attributed to a number of factors including effective primary preventive measures and better treatment options. Developments in revascularization techniques, especially PCI, have influenced its feasibility in cases that would otherwise have been medically/surgically treated. However, the U.S. population is rapidly ageing, resulting in a cohort of survivors at high risk for cardiac comorbidities and subsequent complications, necessitating revascularizations. Paradoxically, the co-existing comorbidities will adversely affect the outcomes.

This dissertation provides the much-needed time-sensitive documentation of changing clinical practice and associated impact on patients, in the real world. The NHLBI-sponsored 1985-86 PTCA and 1997-2004 Dynamic registries were specifically initiated for this purpose and taken together, are one of the few available sources of systematic and comprehensive data to this end. The findings are especially fitting at this juncture wherein the field of PCI appears to be at crossroads - restenosis, the long-time Achilles heel, may have been overcome, but there are emerging concerns of late stent thrombosis and long-term safety.

FUTURE RESEARCH

We now have a snapshot of PCI in the last two decades of clinical practice and its impact on one-year outcomes from two perspectives – the provider (physician) and the receiver (the patient). However, with plateauing of success rates and single-digit restenosis rates becoming a reality [12], it just may be the time to pay closer attention to long-term safety, revisit appropriateness of use and evaluate cost-effectiveness of the procedure.

PCI is probably one of the few fields in clinical medicine, which utilizes new technology with rapid fervor. However, in spite of the overall favorable trends, extensive research is still needed to understand the optimal choice of revascularization procedures in complex anatomy (chronic total occlusions, small caliber vessels, diffuse disease, and bifurcations). A recent report comparing occluded an non-occluded lesions, in the Dynamic registry, showed a decrease in attempts of occluded lesions, with little change in associated success rates [44]. Bifurcation stenting, even with DES, has met with high restenosis rates [91] and is an independent predictor of adverse events in distal left main stenosis.

Approval of stents and other devices follows rigorous evaluation in randomized trials carried out in select, homogenous patient and lesion populations. However, patient profiles in the real world are quite heterogeneous and ~50% of DES implantation occurs in off-label and untested circumstances [16]. The associated concerns of late stent thrombosis [92, 14] and the potential high risk of long-term mortality and Q-wave MI [15] have sparked widespread debate. The role of dual antiplatelet therapy and the uncertainty regarding appropriate duration have also come to the forefront. More recently, one year results from the Clinical Outcomes Utilizing Revascularization and Aggressive DruG Evaluation (COURAGE) trial were made available [93]. This trial, designed to compare PCI + optimal medical therapy with medical therapy alone as

initial management strategy, included 2287 patients with stable CAD followed over 2.5 to 7 years. No significant difference was seen in the primary composite endpoint of death and nonfatal MI with initial strategy of PCI when compared to medical therapy alone. Additionally, although relief of angina was achieved to a greater degree with PCI, substantial improvement was also seen in the medical arm. These results highlight the notable progress in the field of pharmacological therapy, but more importantly, rekindle questions regarding appropriate use of PCI.

Medical decision-making is a complex, multifactorial process with interplay of physician discretion, patient preference and treatment affordability. Durability of treatment benefits relies in effective and continued post-procedural management, including implementation of recommended guidelines for risk factor modification. Patients undergoing PCI are documented cases of CAD and therefore, it is only intuitive that these measures would be effectively stepped up in this cohort. After all, PCI can only treat angiographically visible disease and not the underlying atherosclerotic process that can progress to future lesions. Affordability of health care, a major factor determining continued care, has recently been shown to significantly impact post-procedural health status following revascularization [71]. Even in a field such as PCI, that is expanding its patient (and lesion) base, there exist racial differences in choice of devices (APPENDIX C). With rising healthcare costs and financial barriers impacting healthcare outcomes [94], prescription /recommendation of primary and adjunct therapy do not ensure effective and continued management. Now, more than ever, there is pressing need to ensure appropriate use of available resources by evaluating cost-effectiveness of treatment.

APPENDIX A: TRENDS IN CARDIOVASCULAR OPERATIONS AND PROCEDURES IN THE UNITED STATES (1979-2003)

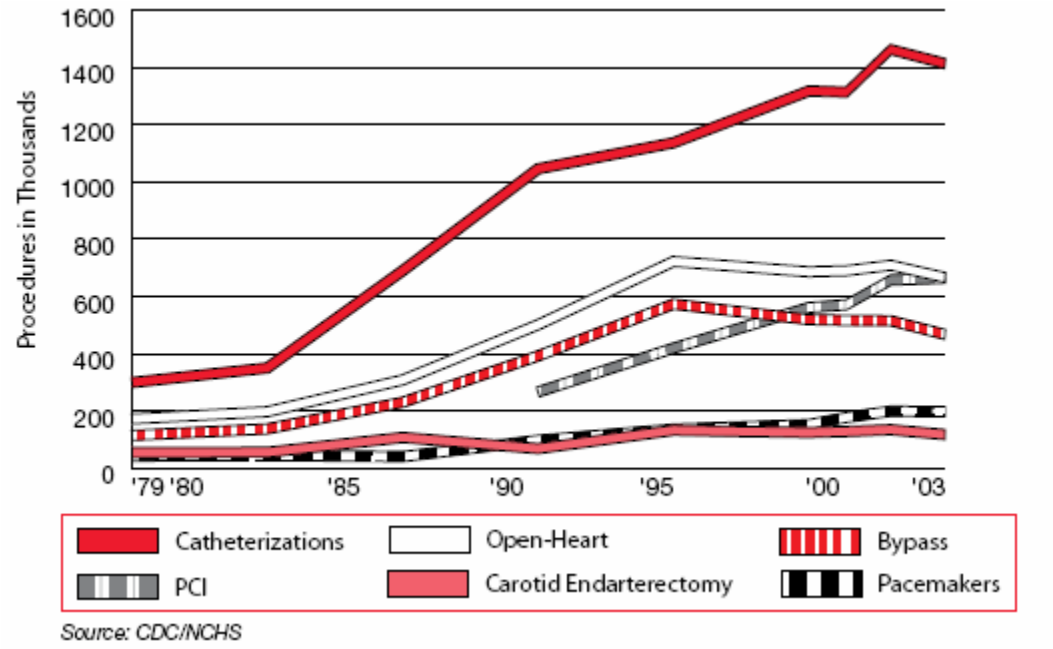


Figure A.1: Trends in cardiovascular operations and procedures in the United States (1979-2003)

APPENDIX B: PARTICIPATING CLINICAL CENTERS IN THE NHLBI-SPONSORED 1985-86 PTCA AND DYNAMIC REGISTRIES

Table A.1: Clinical centers participating in the NH-BI sponsored 1985-86 PTCA and 1997-2004 Dynamic Registries

Boston Medical Center

Cardiovascular Med. Associates, Houston

Emory University

IKEM

Lankenau Hospital

Mayo Clinic

Medical College of Virginia

Montefiore Medical Center

Montreal Heart Institute

New York University – Bellevue

New York University - Tisch

Piedmont Hospital

Presbyterian Medical Center

Providence/St. Vincent - Portland

Rhode Island Hospital

Seton Medical Center

St. Lukes Medical Center

St. Lukes/Roosevelt Hospital - NY

University of Southern California

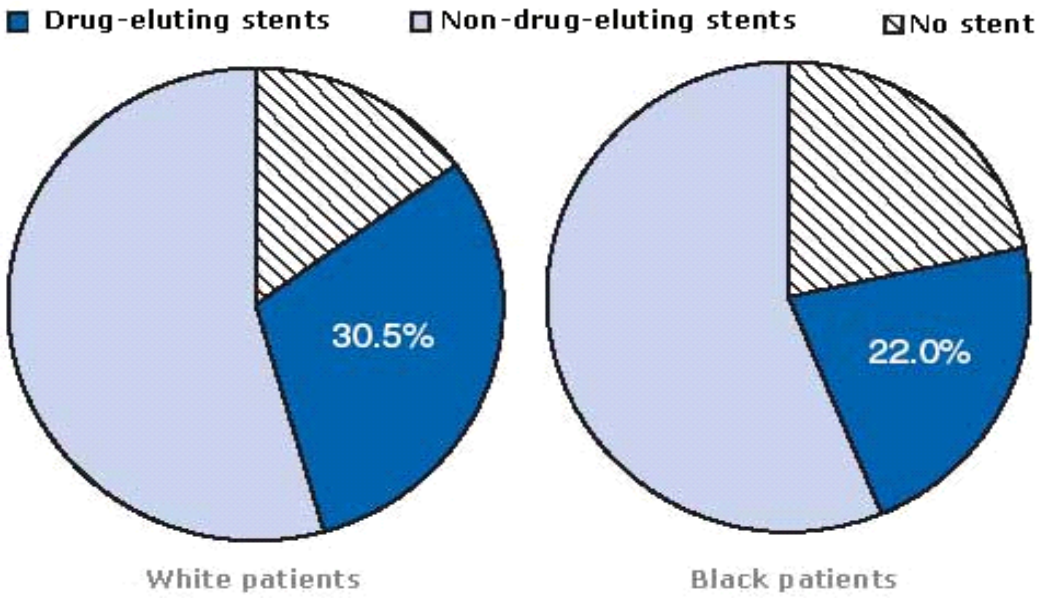
University of Chicago

University of Maryland Hospital

University of Pennsylvania

UPMC Presbyterian University Hospital

APPENDIX C: USE OF STENTS AMONG HOSPITALIZED PATIENTS UNDERGOING CORONARY ANGIOPLASTY, BY RACE, IN THE UNITED STATES (2003)



Source: Morbidity and mortality weekly report [95]

Figure A.2: Use of stents among hospitalized patients undergoing Coronary angioplasty, by Race in the United States (2003)

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