Original article

Outcomes and Excess Costs among Patients with Cardiovascular Disease

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Keywords. Cardiovascular disease; Resource use; Excess costs

Abstract:

Objective: To report on two-year cardiovascular (CV) event rates and quantify the cost of cardiovascular disease using the Australian Reduction of Atherothrombosis for Continued Health (REACH) registry.

Methods: Prospective registry of 2853 patients with multiple risk factors (MRF), coronary artery disease (CAD), cerebrovascular disease (CerVD) and peripheral artery disease (PAD), recruited through 273 Australian general practitioners. Government reimbursement data from 2011 was used to calculate direct health care costs (pharmaceuticals, outpatient and hospitalisation costs). The main outcome of interest was two-year rates and associated excess costs of cardiovascular death, myocardial infarction, stroke, and hospitalisation for cardiovascular procedures.

Results: The two year follow-up data were available for 2856 (99.4%) patients. Incidence of any hospitalisation and cardiovascular death was highest among those with previous history of PAD at baseline 49% (n = 126), and 5.3% (n = 13). Non-fatal cardiovascular events were highest among the PAD and CAD groups (21.8% (n = 56) and 14.3% (n = 297) respectively). Those with previous history of PAD and CerVD at baseline had the highest likelihood of CV death (OR = 2.53 (95% CI: 1.38–4.80) and OR = 1.61 (1.05–2.46) respectively) in comparison to other groups. Patients with PAD had the highest likelihood of vascular interventions OR = 3.11 (95% CI: 2.09–4.63) at two years. Overall, the mean (SD) direct expenditure over two years of follow-up per person was A$7544 (A$1075). In the adjusted model, patients with CAD and PAD incurred A$1093 (95% CI A$24–A$2072) and A$690 (95% CI A$315–A$4869) more in mean total costs compared to patients with MRE.

Conclusions: Patients with PAD had the highest likelihood of vascular interventions and CV death, and incurred high excess costs in comparison to other groups.

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Introduction

Patients with cardiovascular disease (CVD) require significant specialised care [1,2]. In Australia, the direct healthcare costs devoted to CVD amounted to A$11.5 billion in 2011, representing more than 11% of the recurrent health budget [3]. The latest equivalent estimates from the US and Canada are US$448.5 billion and US$52 billion, respectively [4,5].

Although health service use increases with age [6,7] there are relatively few studies reporting service use by older patients with CVD [8–10]. This deficiency is highlighted in the context of a rapidly ageing population. Contemporary data on direct costs for CVD will help inform health policy and health services planning. Ultimately, the goal is to reduce the looming burden of CVD.

We have previously reported an economic analysis of data drawn from one year follow-up of Australian patients in the Reduction of Atherothrombosis for Continued Health (REACH) registry [11]. The current study...
incorporates two-year cost data, estimated from a ‘bottom-up’ approach, and details specific information about prescribed medications, hospitalisations, vascular interventions, and other healthcare services, based on disease severity.

**Materials and methods**

**The REACH registry**

The international REACH registry has been described in detail elsewhere [12]. In short, the REACH registry recruited 67,888 subjects from 44 countries across the world. The sample of Australian REACH registry participants were drawn from general practices across the country and comprised 2,263 participants. Potential candidates were invited to attend initial screening at their usual general practice, where study nurses reviewed their medical records. Participants were recruited consecutively, and every participating general practice recruited a maximum of 15 participants (to limit selection bias) over period of four months from March to June 2004.

**Study population**

The key inclusion criteria were age ≥ 45 years, and either established CVD (of the coronary, cerebrovascular or peripheral arterial beds) or ≥ 3 cardiovascular risk factors.

The risk factors consisted of patients that had documented: diabetes; diabetic nephropathy; ankle-brachial index less than 0.9; asymptomatic carotid stenosis of 70% or more, and carotid intima media thickness of two times or more adjacent sites; systolic blood pressure of 150 mm Hg or higher despite treatment; hypercholesterolaemia, treated with medication, current smoking of 15 or more cigarettes per day, and age ≥ 65 years for men or ≥ 70 years for women.

Coronary artery disease (CAD) was assumed to be present if the participants had one or more of the following: current angina with documented CAD; history of unstable angina with documented CAD; previous coronary angioplasty/stenting; previous coronary artery bypass graft; and previous myocardial infarction.

Cerebrovascular disease (CorVD) was assumed to be present if the participants had either neurologist or hospital report with diagnosis of ischaemic stroke or transient ischaemic attack. Peripheral artery disease (PAD) was assumed to be present if the participants had one or more of the following criteria: current intermittent claudication with ankle-brachial index of less than 0.9 and/or a history of intermittent claudication together with a previous intervention, such as angioplasty, stenting, atherectomy, peripheral arterial bypass grafting, or other vascular interventions, including amputations.

Participants who were hospitalised or were involved in clinical trials at the time of enrolment were excluded from the REACH registry.

**Data collection and evaluation**

Data were collected on an internationally standardised case report form. Baseline information included: demographics, formal education, employment status, previous medical history, risk factors and medications related to cardiovascular disease. Physical examinations were also undertaken and blood sampled for biochemical markers were collected. Participants of the Australian REACH registry were also re-evaluated at 12 ± 3 and 21 ± 3 months to ascertain whether they had experienced any clinical events, hospitalisation, other healthcare services and evaluation of their prescribed medication.

A nurse-review visit was undertaken by trained REACH Registry staff at the GP clinic. Where possible all GP case notes were reviewed and patient-reported hospitalisations were verified against the GP case notes. Patients were either seen at the clinic or interviewed over the telephone if they could not attend the review. In some instances we could not get back into the clinic to follow-up hospital discharges summaries, therefore only what was in the notes was taken (all printed and filed).

Medication data were collected from practice case notes by study nurses and via telephone interview. The prescribed medications and outpatient health service use in the Australian REACH Registry were described in detail in prior work [11].

**Clinical outcomes and hospitalisation**

In the REACH registry, incidents of cardiovascular event were reported by participating clinician-investigators. Data were collected centrally via use of a standardised international case report form. Events were not centrally adjudicated. However, death records and hospital admission records for all cardiovascular events were sourced and verified. Also, cerebrovascular events had to be sourced from a neurologist or hospital to ensure a reliable diagnosis. Cardiovascular death included fatal stroke, fatal myocardial infarction (MI) and any death due to other cardiovascular causes. Any MI or stroke followed by death, whatever the cause, in the subsequent 28 days was considered a fatal MI or fatal stroke. Other cardiovascular death included other deaths of cardiac origin, pulmonary embolism, sudden death including unobserved and unexpected death (for example during sleep), unless proven non-cardiovascular by autopsy, death after a vascular operation, vascular amputation (except for trauma or malignancy), death ascribed to heart failure, death after visceral or limb infarction, and any other death that could not be definitely ascribed to a non-cardiovascular cause or haemorrhage. Non-fatal cardiovascular events included non-fatal MI, non-fatal stroke, unstable angina, transient ischaemic attack, other ischaemic arterial event, congestive heart failure, or an episode of bleeding since 12 and 24 months of follow-up, which lead to hospitalisation and transfusion. Other vascular interventions leading to hospitalisation were classified as coronary artery bypass graft, coronary angioplasty/stenting, carotid surgery, carotid angioplasty/stenting, amputation affecting lower limb, peripheral bypass graft, or any other intervention for PAD.
Cost estimation

Costs were estimated from the perspective of the government, which is the predominant funder of healthcare in Australia. Direct costs that were included in these analyses relate to cardiovascular events. Costs were estimated using a ‘bottom-up’ costing approach, which assign costs to individuals based on specific healthcare item used. This contrasts with the ‘top-down’ approach, which divides total healthcare costs by the number of relevant individuals.

Medication costs were estimated from Australia’s Pharmaceutical Benefit Schedule (PBS) for the period 2010-2011 [13]. Calculation of medication costs have been described in detail elsewhere [11,14,15]. Other healthcare service costs were estimated from Medicare Benefit Schedule (MBS) data for the 2010-2011 period [16]. Hospital costs were based on those assigned to Australian-refined diagnosis related groups 2009 (AR-DRGs) [17] and updated to 2011 values using the total health price index (8.4% increase from 2009 to 2011) [18]. At present, the output of hospitals in Australia is described by 661 separate AR-DRGs [19,20].

Ethics approval

The REACH registry was approved by the Royal Australian College of General Practitioner Research and Monash University Ethics Committee. All subjects gave their written informed consent for participation.

Statistical analyses

Statistical analyses were performed using SPSS for Windows version 19 (SPSS Inc., Chicago, Illinois) and STATA11 (StataCorp, TX, USA). Direct healthcare costs were described both in terms of means with standard deviations and medians with IQRs. These analyses include data related to cardiovascular events only.

Four categories of patients were defined in this cohort, patients with established atherothrombotic disease (CAD, CerVD, and PAD), and patients with multiple risk factors. Categories of patients with CAD, CerVD, and PAD were not mutually exclusive. Therefore, each clinical category was compared against all patients who were not in that category. All patients with a follow-up data at one or two years were included in the analyses (2867 (99.68%) and 2734 (95.73%) respectively).

Multivariable analysis was used to determine the risk of major cardiovascular events and hospitalisation, adjusted for age and gender. The results were reported as adjusted odds ratios (OR).

Table 1. Baseline demographics of patients in two-years of follow-up analysis.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total (n = 2856), n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age mean years (SD)</td>
<td>72.8 (8.9)</td>
</tr>
<tr>
<td>Male</td>
<td>1859 (65.0)</td>
</tr>
<tr>
<td>Unemployed/retired</td>
<td>2313 (81.1)</td>
</tr>
<tr>
<td>Education 1–12 years</td>
<td>1830 (64.3)</td>
</tr>
<tr>
<td>Trade/technical school</td>
<td>556 (19.5)</td>
</tr>
<tr>
<td>College/university</td>
<td>434 (15.2)</td>
</tr>
<tr>
<td>Co-morbidities</td>
<td></td>
</tr>
<tr>
<td>Diabetes*</td>
<td>866 (30.3)</td>
</tr>
<tr>
<td>Hypertension*</td>
<td>2217 (78.7)</td>
</tr>
<tr>
<td>Dyslipidaemia*</td>
<td>2247 (77.6)</td>
</tr>
<tr>
<td>Current smokers</td>
<td>195 (6.9)</td>
</tr>
<tr>
<td>Obesity (BMI&gt;30)</td>
<td>826 (28.5)</td>
</tr>
<tr>
<td>History of CAD</td>
<td>2103 (73.6)</td>
</tr>
<tr>
<td>History of CerVD</td>
<td>667 (23.3)</td>
</tr>
<tr>
<td>History of PAD</td>
<td>257 (9.0)</td>
</tr>
<tr>
<td>Multiple Risk Factors</td>
<td>303 (10.6)</td>
</tr>
</tbody>
</table>


Results

Baseline characteristics

There were 2856 subjects included in the study with 64.5% male and average of 72.8 (8.9) years of age. 58% of participants had CAD without other vascular beds being affected. Overall 15.7% (n = 448) had established polyvascular disease. The combination of CAD and PAD was present in 146 patients (5% of total sample (n=2856)), PAD and CerVD in 15 (0.5%), CAD and CerVD in 259 (9.1%) and all three diseases in 28 (0.9%). The prevalence of diabetes, hypertension and hypercholesterolaemia was high as expected (Table 1).

Two year outcomes: Over two years of follow-up, 37.2% (1061) had one hospitalisation and 6.4% (186) of patients had two hospitalisations. Incidence of hospitalisations and cardiovascular death was highest among those with previous history of PAD at baseline 49% (n = 126), and 5.1% (n = 13). Non-fatal cardiovascular events were highest among the PAD and CAD groups 21.8% (n = 56) and 14.3% (n = 297) respectively. In addition, vascular interventions were more common among those with PAD at baseline.
and 2–3 affected vascular disease location 14% (n = 36) and 7.6% (n = 34) respectively (Table 2a).

Table 2a. Incidence of major events over two-years of follow-up in the REACH Registry.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>MRF (n = 867)</th>
<th>CAD (n = 2203)</th>
<th>PAD (n = 207)</th>
<th>2–3 Disease (n = 448)</th>
<th>MRF (n = 305)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vascular interventions</td>
<td>32 (4.8)</td>
<td>137 (6.5)</td>
<td>36 (14.0)</td>
<td>34 (7.6)</td>
<td>21 (6.9)</td>
</tr>
<tr>
<td>Non fatal events</td>
<td>81 (12.1)</td>
<td>297 (14.1)</td>
<td>56 (21.8)</td>
<td>58 (13.0)</td>
<td>40 (13.2)</td>
</tr>
<tr>
<td>Any hospitalisation</td>
<td>280 (42.0)</td>
<td>917 (43.6)</td>
<td>126 (49.0)</td>
<td>218 (49.0)</td>
<td>109 (36.0)</td>
</tr>
<tr>
<td>CV death</td>
<td>21 (3.2)</td>
<td>56 (2.7)</td>
<td>13 (5.1)</td>
<td>10 (2.3)</td>
<td>5 (1.7)</td>
</tr>
<tr>
<td>Any death</td>
<td>36 (5.4)</td>
<td>99 (4.7)</td>
<td>23 (9.0)</td>
<td>18 (4.0)</td>
<td>10 (3.3)</td>
</tr>
</tbody>
</table>

MRF – multiple risk factors, CAD – coronary artery disease, CerVD – cerebrovascular disease and PAD – peripheral artery disease. 2–3 affected vascular beds.

Table 2b. Risk of major cardiovascular events and hospitalisation over 2 years of follow in the REACH Registry.

<table>
<thead>
<tr>
<th>Type of events</th>
<th>CerVD</th>
<th>CAD</th>
<th>PAD</th>
<th>2–3 diseases</th>
<th>MRF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Odds ratios (OR)</td>
<td>95% CI</td>
<td>Odds ratios (OR)</td>
<td>95% CI</td>
<td>Odds ratios (OR)</td>
<td>95% CI</td>
</tr>
<tr>
<td>Vascular interventions</td>
<td>0.91 (0.59–1.38)</td>
<td>1.50 (0.99–2.26)</td>
<td>3.11 (2.09–4.63)</td>
<td>1.44 (0.97–2.15)</td>
<td>1.21 (0.74–1.97)</td>
</tr>
<tr>
<td>Non fatal events</td>
<td>1.28 (0.97–1.71)</td>
<td>2.06 (1.51–2.81)</td>
<td>2.25 (1.82–3.12)</td>
<td>1.07 (0.78–1.45)</td>
<td>1.04 (0.72–1.49)</td>
</tr>
<tr>
<td>Any hospitalisation</td>
<td>0.92 (0.76–1.11)</td>
<td>0.97 (0.80–1.16)</td>
<td>1.32 (1.01–1.71)</td>
<td>1.21 (1.00–1.51)</td>
<td>0.72 (0.56–0.93)</td>
</tr>
<tr>
<td>CV death</td>
<td>1.61 (1.05–2.46)</td>
<td>1.59 (1.00–2.51)</td>
<td>2.53 (1.56–4.08)</td>
<td>0.86 (0.51–1.44)</td>
<td>0.68 (0.35–1.33)</td>
</tr>
<tr>
<td>Any death</td>
<td>1.75 (1.00–3.04)</td>
<td>1.72 (0.93–3.19)</td>
<td>2.55 (1.37–4.74)</td>
<td>0.84 (0.43–1.67)</td>
<td>0.60 (0.24–1.53)</td>
</tr>
</tbody>
</table>

* Adjusted for age and gender, P-values < 0.05 considered significant. MRF – multiple risk factors, CAD – coronary artery disease, CerVD – cerebrovascular disease and PAD – peripheral artery disease. 2–3 affected vascular beds.

Table 3. Direct and excess costs over two years follow-up.

<table>
<thead>
<tr>
<th>Cost Component</th>
<th>Mean (SD), AUS</th>
<th>Median (interquartile range), AUS</th>
<th>Adjusted mean difference in costs (95% CI), AUS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pharmaceutical costs</td>
<td>MRF (n = 305)</td>
<td>Any CAD (n = 2203)</td>
<td>Any PAD (n = 207)</td>
</tr>
<tr>
<td>Media costs</td>
<td>2646 (1145)</td>
<td>2726 (1152)</td>
<td>2714 (1230)</td>
</tr>
<tr>
<td>Reference costs</td>
<td>2500 (2013 to 3314)</td>
<td>2639 (2032 to 3441)</td>
<td>2694 (1973 to 3534)</td>
</tr>
<tr>
<td>Other healthcare service costs</td>
<td>1414 (944 to 2127)</td>
<td>1423 (947 to 2111)</td>
<td>1489 (1009 to 2057)</td>
</tr>
</tbody>
</table>

Two year costs Two years of follow-up, the average medication cost per person was A$2644 (A$1144). In the adjusted model, patients with CAD incurred A$235 (95% CI A$138 to A$341) more in average drug costs, compared to patients with MRF (Table 3).

Over two years of follow-up, the mean (SD) cost of other health services per person was A$1633 (A$1064). In the adjusted model, patients with PAD incurred A$352 (95%
CI $A170$ to $A625$) more in mean costs compared to MRF group (Table 3). Patients with PAD incurred $A4477$ (95% CI $A2717$ - $A6454$) more in mean hospital costs compared to patients with MRF, while adjusted to all other factors. The differences among other groups were not statistically significant (Table 3).

The mean direct expenditures over two-years of follow-up were $A5754$ ($A10,758$) per person. In the adjusted model, patients with CAD and PAD incurred $A3093$ (95% CI $A24$ - $A2072$) and $A4890$ (95% CI $A3105$ - $A6869$) more in mean total costs compared to MRF patients. After excluding individuals who died over two years of follow up the results were similar (Figs. 1 and 2).

Discussion

Our analyses showed that Australian patients with or at high risk of CVD incurred high public healthcare costs, which was consistent with published findings [8,10,21–23]. The strength of our study is that it comprehensively examines the use of health resources among atherothrombotic patients in different subclinical categories, and provides information regarding recurring hospitalisation and the use of other healthcare services for this group of patients. To our knowledge, this is the first of such analyses in Australia. Furthermore, the application of a ‘bottom up’ costing approach offers a significant advantage in economic studies compared to ‘top down’ approach in terms of accuracy and relevance.

![Fig. 1. Number of patients and total direct cost among the CVD subgroups in the Australian REACH Registry.](image1)

![Fig. 2. Excess total costs among CVD subgroups. Adjusted for age and sex using nonparametric bootstrap 95% CI. MRF – multiple risk factors.](image2)
A previous economic analysis of the Australian REACH registry, based on one-year follow-up data, showed a high annual rate of resource use [11,23], among those with established atherothrombosis disease. The current results extend the previous ones by examining two years of direct health care costs and demonstrate that these costs were very high among PAD patients. The most notable finding was among PAD patients, 49.0% of whom had been hospitalized over the two years and incurred more other healthcare service costs. Greater use of healthcare services is at least partly attributable to a higher observed incidence of acute cardiovascular events. Patients with PAD bear a greater burden of disease; this might reflect a less preventive opportunity, a notion supported by a lesser use of medications in this group [14,24]. For example mean number of medications used for PAD patients was 3.6 compared to CAD patients, 4.5 in the Australian REACH Registry [14]. In addition, these higher event rates may be due to the fact that 74% (n = 189) of patients with history of PAD at baseline had documented disease in more than one location. However, patients with PAD alone were observed to still have higher incidence of any death (10.1%) but experienced lower hospitalisation rates (43.5%) than those for PAD in combination with any other vascular disease location (49.0). Our findings stress the need for intensive management of risk factors, and greater surveillance in general practice (e.g., measuring ankle-brachial indices in general practice). Our findings related to hospitalisation of PAD patients are consistent with recent results reported by the REACH registry [9,10], where PAD patients experienced high cardiovascular event rates and vascular interventions. The cumulative two year cost in the US REACH registry ranged from US$2800 for subjects with claudication and ABI <0.9, to US$11693 for patients with a history of lower limb amputation [9].

This study depicts a government funded healthcare system. The rates of use that were observed in the Australian REACH registry may not reflect what happens in countries with other healthcare funding systems. For example, the rates of use among subjects with atherothrombosis disease in the US might be lower as the access to cardiac procedures and rehabilitation is tied to having private healthcare insurance [25].

This study had a number of limitations in relation to the information collected. Selection bias toward more healthy respondents and limitation of sampling only through GP locations might not directly reflect the prevalence of atherothrombosis in Australian population. Furthermore, this sampling strategy might only underestimate the level of resource utilisation among atherothrombotic population.

In addition, in the Australian REACH registry, healthcare resource use with regard to community-based aged care, or hospitalisation for other non-cardiovascular conditions was not collected. This information might correlate to an underestimation of the true costs of CVD in different clinical sub groups. Other cost data not included in this analysis were patient out-of-pocket costs, which are considered minor in this age category, and indirect costs associated with lost productivity, which are also minor in this group, as 80% of participants were unemployed or retired. However, this information would be necessary to measure the true burden of CVD.

Despite the likely limitations, the data presented here highlights the need for policies that target reducing the number of co-morbidities, such as those that will decrease the incidence of PAD. These findings also highlight that direct healthcare costs among patients with or at high risk of atherothrombosis were high especially for patients with PAD and CAD. The high hospitalisation and vascular intervention cost among patients with PAD are attributed largely due to a very high rate of peripheral revascularisation over two years of follow-up.

Conclusion
Patients with PAD had the highest likelihood of vascular interventions and CV death, and incurred high excess costs in comparison to other groups. These findings can be used to better guide clinicians and the management of patients with systemic disease such as atherothrombosis, and can be used to enhance evidence-based decision-making.

Funding sources
The global REACH Registry is sponsored by Sanofi-Aventis, Bristol-Myers Squibb and the Waksman Foundation (Tokyo, Japan), and is endorsed by the World Heart Federation. The REACH Registry enforces a no-ghost-writing policy. The sponsors provide logistical support. All manuscripts in the REACH Registry are led by independent authors who are not governed by the funding sponsors and are reviewed by an academic publication committee before submission. The funding sponsors have the opportunity to review manuscript submissions but do not have authority to change any aspect of a manuscript. A complete list of the REACH Registry Investigators appears in JAMA. 2006; 295(2): 180–189.

Declaration of conflicting interests
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