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Chronic inotropic therapy in end-stage heart failure

Paul J. Hauptman, MD^a, Peter Mikolajczak, MD^a, Anil George, MD^a, Clinton J. Mohr, MD^a, Robert Hoover, MD, MPH^b, Jason Swindle, MPH^c, and Mark A. Schnitzler, PhD^c

^aDivision of Cardiology, Department of Medicine, Saint Louis University School of Medicine, St. Louis, MO

^bCIGNA Healthcare Medicare Administration, Nashville, TN

^cCenter for Outcomes Research, Department of Medicine, Saint Louis University School of Medicine, St. Louis, MO

Abstract

Background—Interventions in advanced heart failure that provide symptom relief and decrease hospital readmission are important. Chronic intravenous inotropic therapy represents a pharmacologic approach that has been advocated for palliative treatment. However, little is known about associated mortality and cost. Therefore, we sought to describe the impact of chronic infusions on resource use and survival.

Methods—Data were reviewed for a 17-state Medicare region from 1995 to 2002. We obtained hospital and outpatient expenditures accrued up to 180 days before and after the initiation of chronic infusions. Health care use was defined by dollars reimbursed for drug and hospitalizations per beneficiary. Average accumulated cost curves were generated for dollars reimbursed for drug and for hospitalizations by days at risk.

Results—The mean age of the cohort (n = 331) was 69.1 ± 11.3 years. Mortality exceeded 40% at 6 months. Reductions in hospital days were observed at all time points. The amounts reimbursed at 30 and 60 days before and after initiation of inotrope favor drug therapy; however, at six months, the amounts reimbursed were greater due to the cost of milrinone.

Conclusions—Chronic intravenous inotrope use was associated with a high mortality. The cost for milrinone was significant, but there was a decrease in expenditures for subsequent hospitalizations. In the absence of appropriately designed clinical trials, the data suggest that the decision to use inotropes, the choice of inotrope, and the duration of treatment should reflect the impact on resource use.

Congestive heart failure (International Classification of Diseases, Tenth Revision [ICD-10] code I50.0; ICD-9 code 428.0) is a leading cause of morbidity and mortality in older adults.^{1–3} The number of patients aged >65 years admitted with a first listed diagnosis of heart failure increased from 20.3 to 22.1 per 1000 Medicare enrollees from 1990 to 2000.⁴ In the year 2003 alone, 1093000 patients were discharged from acute care hospitals with a diagnosis of congestive heart failure; most were aged ≥65 years.⁵ Heart failure is a common cause for rehospitalization within 30 days in the Medicare population.^{6–8} When the disease progresses to the point that the patient has symptoms at rest despite standard medical therapy, options are limited.

One option, the use of intravenous inotropic drugs, has been part of the treatment of acutely decompensated failure for >2 decades.⁹ The consensus guideline of the American Heart Association/American College of Cardiology¹⁰ classifies the administration of chronic infusions in patients with refractory symptoms as a class IIb indication (“usefulness/efficacy is less well established by expert opinion”) because the effects on morbidity and mortality are not clear.^{11,12} Indeed, several oral inotropes developed in the last 15 years shown to acutely improve cardiac output, decrease filling pressures, and in some cases, enhance quality of life were associated with higher mortality rates when used chronically,^{13–15} raising concerns that intravenous dobutamine and milrinone may also increase mortality. Indeed, one investigator argued “the patients should be fully informed that although inotropic therapy might make them feel better, it also might shorten life expectancy.”¹²

The evaluation of chronic intravenous inotropes has been limited by the lack of well-designed investigations, related in part to practical difficulties encountered in performing placebo-controlled trials in New York Heart Association Class IV patients. Most observational studies have been performed in specialized heart failure centers, raising questions about the general applicability of the results. Further, the studies are seldom powered adequately to lead to definitive conclusions about efficacy and safety.

Therefore, we characterized a Medicare cohort treated with chronic dobutamine, milrinone, or dopamine. We calculated the costs to Medicare associated with this treatment to determine whether expenditures significantly increased or decreased after inotrope initiation. We hypothesized short-term mortality would be high, since 1-year mortality after a heart failure admission in the general Medicare population approaches 40%. Furthermore, we predicted a reduction in the number of hospitalizations after inotrope initiation would decrease the amounts reimbursed by Medicare. This decrease would be only partly offset by the reimbursement for inotrope and associated costs.

Methods

Administrative and limited chart data were obtained from a randomly derived cohort of Medicare beneficiaries from a 17-state region (Alaska, Washington, Oregon, California, Nevada, Utah, Hawaii, Idaho, South Dakota, North Dakota, Iowa, Nebraska, Missouri, Kansas, Wyoming, Arizona, and Montana) and territories (American Samoa, Guam, and Northern Mariana Islands) covered by the Durable Medical Equipment Regional Carrier (DMERC)—Region D for 1995 through 2002. The approximate number of Medicare beneficiaries in each of the four DMERC regions is shown in Table I. The absolute annual number of unique beneficiaries on chronic intravenous inotropic therapy is lower in region D, compared with regions A, B, and C.

Although there was no Medicare drug benefit during the years under study, administration of many intravenous pharmacologic therapies was covered under the Durable Medical Equipment (DME) benefit category when the drug delivery occurred through a chronic intravenous line via an external infusion pump. For heart failure, the DME benefit category covered 80% of outpatient inotropic drug and supplies when both chronic intravenous access was used and acute hemodynamic improvement was demonstrated. Acute hemodynamic improvement was defined as a 20% decrease in pulmonary capillary wedge pressure and/or 20% increase in cardiac index associated with an improvement in dyspnea.¹⁶ In order to manage the program, the Center for Medicaid and Medicare Services (CMS) contracted with regional carriers; the contracted carrier for region D was CIGNA Healthcare Medicare Administration (Nashville TN).

Data were derived from 5 sources: (1) the Health Insurance Claim Form (HCFA-1500), which provides information on beneficiary demographics, secondary insurance, and the unique physician identifier number of the prescribing physician; (2) the Certificate of Medical Necessity (CMN) form, which includes information on the type, duration, and initiation date of inotropic therapy; (3) the Data Collection Form, which includes clinical data on the beneficiary's hemodynamic profile and extent of acute improvement in cardiac index and pulmonary capillary wedge pressure at the time of inotrope prescription; (4) the Beneficiary Update and Display System financial data form, which itemizes amounts charged and reimbursed (at 80% of usual and customary charges) for outpatient drug and supplies; and (5) Health Insurance Master Record for hospitalizations.

For each beneficiary, the amount reimbursed by CMS for outpatient inotrope therapy was calculated, starting at the date of CMN and ending with the date of death or DMERC's last day of contact (defined by the last recorded date of service provided for the patient as of December 5, 2005). Furthermore, we calculated hospital and miscellaneous outpatient expenditures accrued 180 days before and after the CMN date. The amounts reimbursed per beneficiary were adjusted to the 2002 Consumer Price Index (<http://data.bls.gov/cgi-bin/surveymost?cu>).

We assessed healthcare use by describing cost and hospitalizations in dollars and days respectively, per beneficiary, controlled for duration of follow-up by censoring on date of death or last date of contact. Average accumulated costs over time¹⁷ were calculated for both inotropic therapy and hospitalizations before and after the date of therapy initiation.

The amounts reimbursed for each drug were independently evaluated; if an inotrope was switched or if a second inotrope were added, the initial drug was considered to be the primary treatment by intention-to-treat methodology. Two patients were initially treated with both milrinone and dobutamine; because the former was used for a longer period, these cases were assigned to the milrinone cohort. We did not include data for dopamine because its use was limited to 2 patients, totaling <\$125. Furthermore, we compared patients on dobutamine and milrinone with respect to demographics, medications, and hospitalizations before inotrope initiation.

The asymptotic distribution for cost curves, as we have derived them, has not been established. Therefore, analytic CIs are not available. Instead, we used bootstrapping to derive standard errors and CIs from these calculations.

Data management and analyses were performed using SAS 9.1 (Cary, NC). Abstractor reliability measures were obtained using SPSS 13.0 (SPSS, Chicago, IL). κ statistic was used for categorical variables and intraclass correlation coefficients for testing continuous variables¹⁸; values ranged from 0.63 for date of birth to 1.0 for primary ICD-9 diagnosis, date of initiation, selection of inotrope, and reimbursed dollar amounts for drug and pump.

Original records were maintained at the carrier (CIGNA); vital information was available for 65.8% of beneficiaries over the 8-year period. Data were missing largely as a result of nonsystematic purging of files. All efforts were expended to locate records on missing beneficiaries; no pattern of missing records by state or year was identified. Unique beneficiary identifiers (including the Health Insurance Claim number) were redacted from the records according to the data user agreement between the investigator (PJH) and CIGNA Healthcare Medicare Administration. As such, we were unable to review the date of death using the social security death index when the date of death was missing from the Health Insurance Master Record form. The study was approved by the Saint Louis University Institutional Review Board.

Results

Demographics and patient characteristics

A total of 331 beneficiaries (73.4% male, mean age 69.1, SD/11.3 years) with records from calendar years 1995 to 2002 inclusive received ≥ 1 inotropic drugs by continuous (89.7%) or intermittent (10.3%) infusions. None of the beneficiaries were aged >90 years; 13.6% were aged ≥ 80 years. The patients were initiated on dobutamine ($n = 255$) or milrinone ($n = 74$) or both ($n = 2$). During subsequent follow-up, changes in therapy occurred in 13 (3.9%) (Figure 1).

Background medications used at the time of inotrope initiation were available in 312 patients and included angiotensin converting enzyme inhibitor (35.6%), angiotensin receptor blocker (9.6%), β -adrenergic blocker (15.1%), digoxin (39.7%), nitrates (14.3%), and spironolactone (11.5%). β -Blocker use increased from $<2\%$ in 1995 to 1997 to 7.2% in 1998 to 1999 and 21.8% in 2000 to 2002. Patients on milrinone were more likely to be on digoxin (49.3% vs 36.7%, $P = .051$), but there were no other differences between the 2 inotrope groups with respect to background medication.

Most prescribers were cardiologists (81.6%) or internists (12.1%). A small percentage (1.8%) included other specialties (eg, anesthesiology); specialty could not be confirmed in 4.5%. The beneficiaries were distributed across the entire DMERC region, including California (35.4%), other Western states (22.7%), and the Midwest (36.3%), with data unavailable in the remaining 5.6%. There was a higher likelihood of milrinone use in the Midwest (48.7% vs 32.6%, $P = .004$ by analysis of variance) but no difference in drug selection by patient age, sex, or prescriber type.

Hospitalization and survival

The average number of days hospitalized per beneficiary per month before and after inotrope initiation is shown in Table II. Patients initiated on milrinone were hospitalized on average 13.9 days in the preceding 30-day period, compared with 13.0 days for patients initiated on dobutamine. The median time between antecedent hospitalization and inotrope initiation was 40 days for dobutamine and 48 days for milrinone. Heart failure (*ICD-9 428.x*) was the most common primary cause of hospitalizations before and after initiation of inotropic therapy, although milrinone patients were more likely to have been hospitalized with heart failure in the 30 days preceding inotrope prescription.

After drug initiation, there were reductions in days hospitalized at all 3 time points (30, 60, and 180 days), with similar reductions for dobutamine and milrinone. The percentage of admissions attributed to heart failure declined in both groups, and there was no increase in admissions for atrial or ventricular arrhythmias.

There was a significant early mortality at 6 and 12 months (42.6% and 56.8% respectively; see Figure 2); however, 21.8% and 8.7% of beneficiaries survived >3 and >5 years, respectively. Long-term survival (>5 years) was not related to initial inotrope used (χ^2 by log-rank test 0.15, $P = .7$) or sex (χ^2 by log-rank test 2.17, $P = .14$); however, age of patient (<65 vs ≥ 65 years) was associated with a better prognosis ($\chi^2 = 4.94$, $P = .026$).

Cost

The amounts reimbursed for inotrope and supplies per beneficiary (not corrected for differential follow-up) were largely reflective of the inotrope cost. The mean (and median) amounts for dobutamine, milrinone, and supplies were \$5025 (1168), \$87781 (31440), and \$7284 (3131), respectively.

In terms of health care use (excluding professional and nursing fees), the amounts reimbursed at 30 and 60 days before and after inotrope initiation favor drug therapy; however, among patients who survived 6 months, the amounts reimbursed at 180 days were greater after inotrope initiation (Table III). Similar trends are seen on a per-beneficiary-per-day basis although the amounts were lower per diem the longer the beneficiary survived on inotrope (Table IV). The greater amounts reimbursed at 180 days were driven by the cost of milrinone; the average accumulated drug cost curve for inotrope demonstrates a significant difference between dobutamine and milrinone (Figure 3).

Hospital costs remained lower after inotrope initiation at all time points except among patients on milrinone at 180 days: there was a net increase of \$311793 for the cohort as a whole and \$83.06 on a per-beneficiary-per-day basis. The average accumulated hospitalization cost curves by drug type up to 180 days are shown in Figure 4. Compared to dobutamine, milrinone was associated with statistically greater hospitalization costs after the initiation of inotrope at all time points extending to 1 year ($P < .01$ at 30, 60, 180, and 365 days). For example, average accumulated hospitalization costs for dobutamine and milrinone were \$25019 (95% CI 23716–26323) and \$49860 (95% CI 45752–53968), respectively, at 180 days; the comparable figures at 1 year were \$43144 (95% CI 40508–45780) and \$68185 (95% CI 62720–73649).

Intermittent versus continuous infusions

The cohort receiving intermittent infusions was older (74.2 SD/9.0 vs 68.5 SD/11.4 years, $P < .01$) and more likely to be taking hydralazine but, otherwise, did not differ by region, background medication, or inotrope type. Inotrope costs were greater for beneficiaries receiving continuous infusions. There was a nonsignificant greater average number of days hospitalized per beneficiary per month among the continuous group but no difference in mortality.

Discussion

The aging population, increasing prevalence of chronic congestive heart failure among older persons, and increasing health care cost concerns have stimulated attempts to assess the care delivered to patients with advanced heart failure. One treatment option, chronic infusions of intravenous inotropic drugs, has not been subjected to large double-blind, randomized clinical trials nor are there published data to suggest this therapy improves survival in any age group. In fact, there is concern that chronic inotrope infusions increase mortality.^{11,12,19–22} Nevertheless, despite the lack of definitive data, the therapy is recognized in American Heart Association/American College of Cardiology guidelines as a treatment option for select patients.¹⁰ Because epidemiologic studies show that the prevalence of heart failure is increasing in the Medicare population,^{4,23,24} it is likely that the cohort of patients potentially eligible for this therapy is increasing. Furthermore, with the wider use of implantable cardioverter-defibrillators, the population of patients progressing to refractory symptoms and dying from progressive pump dysfunction, rather than sudden death, may continue to increase.²⁵

Any intervention in advanced heart failure that provides symptom relief and decreases hospital readmission rates is important. In this context, our study was designed to describe Medicare patients treated with chronic outpatient inotropic therapy (either continuous or intermittent) and the reimbursement for both drug and supplies.

We demonstrate that the mortality rate associated with patients receiving this therapy is very high, although not to the level observed in patients treated with inotrope and optimal medical management in the REMATCH study.^{26,27} The cost and number of days of hospitalization are lower after inotrope initiation, compared with the same period before therapy. However, because of the high cost of milrinone (a branded drug during most of the period under study),

combined costs for hospitalization, drug, and supplies are greater in total and on a per diem basis at 6 months. Indeed, milrinone expenditures accounted for most of the cost of this DME benefit.

The population treated with milrinone had higher amounts reimbursed for hospitalizations before and after inotrope initiation. In addition, the background use of digoxin was greater in the milrinone group. Whether these patients were more ill cannot be determined from these retrospective data; however, survival after inotrope initiation was not different between the groups.

Background therapy was significant for apparent underuse of both angiotensin-converting enzyme inhibitors and β -blockers; however, no conclusions can be drawn about the appropriateness of this treatment, given the severity of illness and the likelihood that many of the patients were intolerant of the drugs because of low cardiac output syndrome, hypotension, or other comorbidity.

This is the largest series of chronic intravenous inotropic therapy reported to date. Prior publications have been limited to single center and other small series,^{28,29} reports about inotropic therapy as a bridge to transplant,^{30,31} or intermittent therapy.^{32–34} One multicenter trial evaluated empirical milrinone early after admission for decompensated heart failure,³⁵ but the patients were not generally considered end-stage.

Our results are comparable to those of Harjai et al³⁶ who demonstrated significant reductions in hospital costs after inotrope initiation; however, drug costs were not considered. In a series of patients receiving home health care for heart failure, Wilson et al²⁸ describe a cohort of 10 patients who received chronic intravenous inotropic therapy during the period 1995 to 1996; costs for drug therapy (not otherwise specified) were $\$1382 \pm \722 per week. Aranda et al³¹ demonstrated a large drug cost differential between dobutamine and milrinone in a cohort of patients listed for transplant and randomized to these agents. Hershberger et al reported their experience with 36 stage D patients who failed inotrope weaning.³⁷ The 6-month mortality rate was 74%; hospitalizations were reduced, but this may reflect the fact that the majority of patients opted for home care. In general, the patients in these studies also receive a home nursing intervention, which may decrease the likelihood of hospitalizations caused by noncompliance and related factors.⁸ In our series, some patients may have been transitioned to hospice care, although the cost of palliative inotropic therapy is a barrier to hospice referral.³⁸

Limitations

Our analysis is limited by the absence of a hospitalized Medicare heart failure control group not treated chronically with intravenous inotropic therapy. Even with each subject serving as his/her own control, bias is implicit in that the very reason for initiation of inotropic therapy may have been an attempt to decrease hospitalizations and associated health care resources. Only a prospective, randomized, double-blinded trial could realistically answer questions about mortality and costs. Such a trial would be challenging because crossover to active therapy would likely occur in a significant proportion of patients. Furthermore, there are no data that address the appropriateness of inotrope prescription or the selection of the particular drug.

We do not have data on the financial burden on patients. Payment by Medicare is according to “reasonable and customary” charges. In many instances, beneficiaries are responsible for 20% of these charges. Furthermore, part B data and home health and laboratory costs were not available and, hence, we did not capture all the resources expended.

It is also unclear if beneficiary demographics and CMS expenditures in region D are similar to the 3 other DMERC regions. However, the number of beneficiaries in these latter regions

receiving intravenous inotropic therapy are greater, and we did not have financial data on the full region D cohort. Therefore, our cost estimates likely represent less than a quarter of the financial burden to CMS of chronic inotrope treatment.

Since the analysis covers a period when milrinone was branded, costs today would be lower. According to industry figures,³⁹ the average wholesale price for 10 10-mL vials containing 1 mg/mL of milrinone increased from \$613.32 in 1996 to \$896.76 in 2002; approximately 5 vials are used per day for an average 70-kg individual. The generic version, first available in mid 2002, had a price of \$763.80 (or 85.2% of the branded price). In contrast, the price of generic dobutamine has remained relatively constant during the same period. The average wholesale price for ten 20-mL vials containing 12.5 mg/mL of dobutamine ranged from \$54 to \$210 depending on manufacturer; approximately 4 vials are used per day for an average 70-kg individual. Therefore, the costs of generic milrinone remain high, relative to dobutamine. It is also likely that any new drug developed for the treatment of decompensated heart failure would be priced higher than generic milrinone. If such therapy were to be considered “reasonable and necessary” by CMS, costs of chronic intravenous therapy would be at least as high as what we observed in the cohort treated with milrinone. Therefore, the data presented represent a reasonable facsimile of the economics of chronic intravenous infusions when a generic formulation is unavailable.

Finally, we can draw no conclusions about the practice of intermittent inotropic infusions because this approach was used in few beneficiaries. Current American Heart Association/American College of Cardiology guidelines classify this approach as a level III recommendation (“conditions for which there is evidence and/or general agreement that a procedure/treatment is not useful/effective and in some cases may be harmful”).¹⁰

Future directions

The costs associated with home inotropic therapy can be compared to those accrued in a Medicare control group not treated with chronic infusions but matched for age, date of hospitalization, and number of antecedent heart failure hospitalizations in the 6 months before the index hospitalization. This retrospective case-controlled study would further gauge the financial impact of this therapy in the absence of evidence of long-term benefit. In addition, examination of regional differences can be analyzed; however, as exemplified by region D, there is no clear geographic pattern to the different regions covered by the 4 DMERCs. Greater insight into the type of patients selected for inotropic therapy and outcomes could be obtained by use of a registry, preferably with national representation of patients. However, funding is likely to be an issue as the current agents approved for use by CMS are all available in generic form.

Conclusion

The use of chronic intravenous inotropic therapy in a Medicare cohort is associated with high mortality, likely reflecting the severity of the underlying disease. The costs associated with heart failure management in both inpatient and outpatient settings are significant; the latter is driven by the cost of milrinone. Nevertheless, there is an early decrease in overall expenditures after inotrope initiation, attributable to a reduction in hospitalization. Given the absence of double-blinded trials comparing inotrope infusion to placebo or dobutamine to milrinone, the decision to use inotropes, the choice of inotrope, and the duration of treatment should reflect the impact on resource use.

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Figure 1.
Flow diagram demonstrating different drug combinations.

Figure 2.
Kaplan-Meier survival curves.

Figure 3.
Average accumulated drug cost curve.

Figure 4.
Average accumulated hospitalization cost curve by drug type.

Table I

Medicare enrollees by Region (2002)

DMERC region	Population	Medicare enrollees	% of Population enrolled
A	55035000	8295000	15.1
B	65817000	9109000	13.8
C	88101000	12044000	13.7
D	73740000	9279000	12.6

Table II

Average number of days hospitalized per beneficiary per month before and after initiation of inotrope

No. of days	All INO		Dobutamine		Milrinone	
	Pre-CMN	Post-CMN	Pre-CMN	Post-CMN	Pre-CMN	Post-CMN
30	13.3	4.4	13.0	4.3	13.9	4.7
60	8.7	4.0	8.6	3.8	8.9	4.4
180	4.2	2.3	4.2	2.2	4.3	2.9

Table III

Health care use at 30, 60, and 180 days

	All INO		Dobutamine		Milrinone	
	Pre-CMN	Post-CMN	Pre-CMN	Post-CMN	Pre-CMN	Post-CMN
30 d	n = 320	n = 331	n = 246	n = 255	n = 74	n = 76
Person days	9226	9214	7090	7041	2136	2173
Hospital cost (\$)	5453726	2033818	3900395	1337708	1553331	696109
INO cost (\$)	0	1176680	0	202159	0	974521
Supply cost (\$)	723	309262	275	225302	448	83960
Total cost (\$)	5454449	3519760	3900669	1765169	1553780	1754590
60 d	n = 297	n = 287	n = 228	n = 218	n = 69	n = 69
Person days	17940	17164	13789	13139	4151	4025
Hospital cost (\$)	7419823	3754820	5548634	2305655	1871189	1449164
INO cost (\$)	0	1967432	0	365317	0	1602115
Supply cost (\$)	4020	529136	916	388590	3104	140546
Total cost (\$)	7423844	6251388	5549550	3059562	1874294	3191826
180 d	n = 283	n = 262	n = 217	n = 202	n = 60	n = 60
Person days	50462	41766	38789	32325	11673	9441
Hospital cost (\$)	10159765	7045610	7689625	4263677	2470140	2781933
INO cost (\$)	0	4179268	0	813734	0	3365534
Supply cost (\$)	5618	1096565	1466	817792	4153	278773
Total cost (\$)	10165383	12321443	7691091	5895203	2474292	6426241

INO, Inotrope.

Table IV

Health care use at 30, 60, and 180 days on a per-beneficiary-per-day basis

	All INO		Dobutamine		Milrinone	
	Pre-CMN	Post-CMN	Pre-CMN	Post-CMN	Pre-CMN	Post-CMN
30 d						
Hospital cost (\$)	591.13	220.73	550.13	189.99	727.21	320.34
INO cost (\$)	0.00	127.71	0.00	28.71	0.00	448.47
Supply cost (\$)	0.08	33.56	0.04	32.00	0.21	38.64
Total cost (\$)	591.20	382.00	550.16	250.70	727.42	807.45
60 d						
Hospital cost (\$)	413.59	218.76	402.40	175.48	450.78	360.04
INO cost (\$)	0.00	114.63	0.00	27.80	0.00	398.04
Supply cost (\$)	0.22	30.83	0.07	29.58	0.75	34.92
Total cost (\$)	413.82	364.22	402.46	232.86	451.53	793.00
180 d						
Hospital cost (\$)	201.33	168.69	198.24	131.90	211.61	294.67
INO cost (\$)	0.00	100.06	0.00	25.17	0.00	356.48
Supply cost (\$)	0.11	26.25	0.04	25.30	0.36	29.53
Total cost (\$)	201.45	295.01	198.28	182.37	211.97	680.67